EXHIBIT A

HARVEY

SUPERIOR COURT

JUDICIAL DISTRICT OF HARTFORD

(COMPLEX LITIGATION DOCKET)

Docket No. X03-HHD-CV-15-6057664-S

EDWARD McDEVITT,)
Plaintiff,)
v.)
BOEHRINGER INGELHEIM PHARMACEUTICALS,)
INC., and BOEHRINGER INGELHEIM)
INTERNATIONAL GmbH,)
Defendants.)

DEPOSITION OF BRIAN E. HARVEY, MD, PhD

Washington, D.C.

November 30, 2017

Reported by: Mary Ann Payonk

Job No. 132828

HARVEY

November 30, 2017
8:30 a.m.

Deposition of BRIAN E. HARVEY, MD, PhD, held at the offices of Covington & Burling, 850 Tenth Street, N.W., Washington, DC, pursuant to Notice before Mary Ann Payonk, Nationally Certified Realtime Reporter and notary public of the District of Columbia, Commonwealth of Virginia, and State of New York.

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APPEARANCES:

ON BEHALF OF PLAINTIFF:
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ON BEHALF OF DEFENDANTS:
PAUL SCHMIDT, ESQUIRE
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ALSO PRESENT:
Kim Johnson, videographer

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THE VIDEOGRAPHER: Here begins media number 1 in the video recorded deposition of Dr. Brian Harvey, taken in the matter of Edward McDevitt versus Boehringer Ingelheim Pharmaceuticals et al., in the Superior Court, Judicial District of Hartford, Case Number X03-HHD-cv-15-6057664-S.

Today's date is November 30, 2017. The time is 8:51 a.m. This deposition is being held at 850 10th Street Northwest, Washington, D.C.

The court reporter is Mary Ann Payonk, the video camera operator is Kim Johnson, both on behalf of TSG Reporting.

Will counsel please introduce yourselves and state who you represent.

(Whereupon, counsel placed their appearances on the video record.)

THE VIDEOGRAPHER: The reporter may swear the witness.

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DR. BRIAN HARVEY,
called as a witness, having been duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. SCHMIDT:

Q. Dr. Harvey, thank you for joining us today. We said hi briefly before. I'm Paul Schmidt, I represent Boehringer in this case, and I understand you're a retained expert for the plaintiff in this case.

A. Yes, that's correct.

MR. SCHMIDT: We have a lot to cover given the size of your report, so let me jump in. I put before you what I've marked as Exhibit 1, which I understand to be a copy of your 120-page report.

(Harvey Exhibit No. 1 was marked for identification.)

BY MR. SCHMIDT:

Q. Is that a correct description of it?

A. From a look at the beginning and the end, it appears to be my report, yes.

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Q. I have not slipped stray pages in.
A. Okay.
Q. I'm sure Mr. Moskow would tell me if I had. This report that we've marked as Exhibit 1 contains all your opinions in this case; correct?
A. That's correct.
Q. You're ready to give those opinions and you've done the work you need to be able to explain them?
A. Yes, I have.
Q. If you were going before a jury now, you'd be ready to testify in front of a jury?
A. I'd be ready.
Q. There's no additional work you've either done or plan to do, is there, in terms of generating new opinions?
MR. MOSKOW: I would just object to the point that we received new documentation on Tuesday night from Mr. Hudson that we've not shared with the witness, and we reserve the right to share and seek further information from him after today's deposition.

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MR. SCHMIDT: If you do that I'd ask you to let us know and we will ask to take Dr. Harvey's deposition again.
MR. MOSKOW: We can address that if and when.
THE WITNESS: AND I would be happy to make myself available if that was the case.
MR. SCHMIDT: Thank you, Doctor. I appreciate that.
Q. Is there anything right now that you know of that you need to do in addition to the work you've done preparing your report?
A. Well, based upon my experience at FDA, new data does appear. You know, there are new publications. And this is a case where the data has evolved over time. So if between now and trial there was a release of new data, new publications, then I would certainly be looking at that, and then I would discuss with counsel the best way to make sure that that information got incorporated.
Q. I understand your point on that. There's no new data you know of right now

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that's not reflected in your report that you intend to rely on, is there?
A. Not that I know of.
Q. Okay.
MR. MOSKOW: As supplemented with the additional materials.
MR. SCHMIDT: Yeah.
Q. You mentioned just before we were on the record your experience at the FDA. And I take it that's something that you would say is part of the reason you can serve as an expert witness in this case. I want to ask you a couple questions about the FDA.
Would you agree with me that the FDA has closely reviewed the safety and efficacy of Pradaxa since before it was launched up through the present date?
A. Well, if you could just clarify on your question, because there -- if one is on the outside, there's no way to know the intensity of any specific review. So from the outside, yes, they follow the traditional FDA process which led to the NDA approval, but there's no way to know whether any individual

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reviewer analyzed every topic and every concern from the outside.
Q. Doctor, you've not seen the publications by FDA officials on Pradaxa?
A. Yes, I have.
Q. You've not seen the communications back and forth between the FDA and individuals at Boehringer?
A. Yes, I have.
Q. You've not seen the review memos written by individuals at the FDA and comments they've made on labeling and things of that nature?
A. I've seen the review memos.
Q. And you've not seen the public statements that FDA officials have made regarding Pradaxa?
A. Yes, I have.
Q. From those various materials that you have seen, would you agree with me that the FDA has closely looked at the safety and the efficacy of Pradaxa from before it was approved up through the present date?
A. Based upon that information that

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you've just cited, they've done a review of Pradaxa.

Q. Has it been thorough?

A. Once again, there's a -- I'm having difficulty with the word "thorough" because it's not defined in regulatory terms. And given the fact that there are some concerns with the drug, it was not a perfect review.

Q. Okay. What were the flaws in the FDA's review from your perspective?

A. Well, that's part of my opinions in my report, which I'm happy to go over.

Q. What did the FDA get wrong in your view on Pradaxa?

A. So as -- going back to the initial data set with the initial interpretation, because just to clarify, as you know, based upon the publications, there was a reanalysis of the RE-LY data that was published and then there was another reanalysis later on, and there was the data before the refuse to file by FDA, and then there was the data after the refuse to file.

So based upon that early data, there

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was always a concern that having a policy of no monitoring across the board didn't necessarily fit with the data. And in the RE-LY trial, there had been a concern that there may not have been enough patients that fit into all the different subcategories where they would -- may have been at higher risk in order to fully test the working hypothesis that the sponsor had that no monitoring was valid across the board.

So a concern of the trial and a concern of FDA's review is that in many of their documents and public statements, they focused on stroke prevention, and yet trying to minimize risk by minimizing both GI bleeding and non-GI bleeding appeared to be secondary in their thinking. And some of the tools that I would have thought they would have used and actually later were in Bob Temple -- so Dr. Robert Temple, who has several roles at FDA, has since come out with some slide sets, and he actually has mentioned certain things -- and I'm sure we will talk about that.

But all of that information or all of those concepts could have come into play during

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the initial FDA review. And based upon the materials I've seen, they haven't.

Q. Okay.

A. So RE-LY was a good first step, but either there should have been more with RE-LY or subsequent trials should have addressed the questions, some of which are still unanswered as of today.

Q. So let me see if I can unpack that very long answer.

Do you fault the FDA for approving Pradaxa without a monitoring requirement, based on the data that they had at that time?

A. If you define monitoring as routine monitoring as is done traditionally with Coumadin, I don't believe that routine monitoring is the answer. I believe in dose adjustment. So of course the answer to that then would be yes, the way you phrased the question.

Q. You do fault the FDA?

A. No, I don't fault the FDA.

Q. Okay. Should the FDA have required some form of blood testing with Pradaxa in your

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view?

A. Given that FDA was looking at benefit/risk, I think there were several different paths forward. If they were not going to approve the 110 dose, then there would have been more of an emphasis on monitoring. If they had had a 150 dose and a 110 dose, then testing would have allowed a dose reduction in an appropriate systematic manner.

So it's really a combination of testing individuals, you know, tailoring the treatment to the individual, because one size doesn't fit all, but second of all, having then the option of dose reducing from the 150 to the 110 dose which, you know, did not get approved. By not having that option, you know, that was a -- I think a limitation in FDA's review and a potential blind spot.

Q. I'm going to get into detail on a lot of those points. I just want to ask you some simple questions just at the outset.

Do you agree or disagree with the FDA's decision not to approve the 110 dose? Or do you not have a position on that?

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A. Well, I can understand why they didn't --

Q. I'll withdraw my question. I'm just going to ask you a yes or no question.

A. Okay.

Q. We've got a lot to cover and I'm going to get into detail on some of these points and you'll have a chance to talk about them and you've had a chance to talk about them in your report. But I want to just see if I can just understand the parameters of your opinion.

A. Okay.

Q. So let me, with that said, ask my question.

MR. MOSKOW: Let him ask the question. And also, if you're not able to answer yes or no, you need to tell him that.

THE WITNESS: Okay.

Q. My question is simply, do you agree, disagree or not have a view on whether the FDA appropriately declined to approve the 110? Agree, disagree or don't have a view?

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A. I believe they should have approved the 110 dose based upon the information I've reviewed.

Q. Do you agree, disagree or don't have an opinion on whether the FDA was correct in approving Pradaxa 150 with no form of blood concentration monitoring requirements at all? Agree, disagree or don't have a view?

A. I agree with the approval.

Q. Under those terms?

A. Not under the label that they approved but I agreed with the product approval at 150.

Q. Do you agree with the product approval of 150 with no blood monitoring requirement?

A. With no blood monitoring requirement, yes, I agree with that.

Q. Okay. Let's go ahead and mark your --

A. But I do make that distinction between routine monitoring and dose adjustment. I --

Q. Do you agree or disagree with the

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FDA's approval of the launch label for Pradaxa?

A. I disagree with the launch label.

Q. And I take it you disagree with FDA on -- from your report you disagree with the FDA on its approval of every version of the Pradaxa label. True or false?

A. That's true.

MR. SCHMIDT: I'm going to go ahead and mark as Exhibit 2 your CV. And I'll spend some time asking you some questions about your CV.

(Harvey Exhibit No. 2 was marked for identification.)

BY MR. SCHMIDT:

Q. Is this the most current version of your CV?

A. This is an up-to-date version of just my basic CV.

Q. Is there a more expansive version?

A. I think I shared -- I have -- there are more expansive versions and -- with just more detail about -- around this skeleton. And it's also publicly available on my LinkedIn --

Q. The more expansive version is?

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A. I think there's more detail.

Q. Okay.

A. This is the version I routinely give out to people because I believe in clarity and brevity.

Q. Just like the FDA; right? Correct?

MS. PRESBY: Objection.

A. Is that a real question?

Q. It is a real question. The FDA has that principle in labeling, don't they?

MR. MOSKOW: Objection to form.

Q. Clarity and brevity in labeling?

A. That's one of their stated goals on the website.

Q. If we look at Exhibit 2, Exhibit 2 reflects that you've been medically trained in gastroenterology; correct?

A. That's correct.

Q. But you've never had a full-time gastroenterology practice?

A. That's correct.

Q. As I understand it, you've never had a full-time medical practice of -- at any point in your career?

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A. That's correct.

Q. You did practice while you were at the FDA kind of, I guess, on evenings and weekends; is that right?

A. Right. 20, 25, 30 hours a week as a medical hospitalist.

Q. And that stopped in 2010?

A. Yes. So after I left FDA in 2007 I went to work for Sanofi. And just given my duties at Sanofi and the travel, it became very difficult to schedule time. So eventually I stopped that practice.

Q. So when did your medical practice -- when did you last practice medicine?

A. So 2010.

Q. 2010? Are you currently licensed?

A. Yes, I am.

Q. But you're not a practicing physician as we sit here?

A. I do volunteer work internationally, and so I've kept up my medical license, including continuing medical education and all of the different things because I believe in giving back, so I do travel around the world

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and I've done some medical work and also some veterinary work with my wife, who's a veterinarian.

Q. How often do you do that?

A. One or two times a year.

Q. Does your wife have a private practice?

A. My wife, who was at FDA as well when I was there, but in devices, works as a medical device consultant, but she does have a part-time -- she works in a practice in Maryland, not as an owner but as an employee, part-time, and she also does work for the SPCA and then World Vets internationally.

Q. Is her device practice focused on veterinarian devices?

A. It's on human devices.

Q. On human devices?

A. Yeah.

Q. Has she done any work that touches on any issues relevant to this case in terms of assays or bedside devices?

A. Her focus are vascular stents, so at FDA she was an expert in coronary stents and

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carotid stents. So her focus has been 510(k), PMA and peripheral vascular stents. So she's dealt with cardiologists but from a -- in the stenting, interventional community.

Q. Let's go back to your experience. Have you ever diagnosed atrial fibrillation?

A. Yes, I have.

Q. When did you last do that?

A. I actually did that in my father three years ago.

Q. Is your father -- not going to ask you about that. When was the last time you diagnosed atrial fibrillation as part of your medical practice?

A. 2010.

Q. 2010? And have you treated atrial fibrillation?

A. During my work at Anne Arundel Medical Center as a medical hospitalist.

Q. And how have you treated it?

A. Well, it depends on whether it's new or -- I mean, my role as a medical hospitalist is after a patient, let's say, was in the emergency room and got diagnosed and the

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decision made to admit them, I would admit them to the hospital. So -- and then I would develop a treatment plan, and more often than not a cardiologist would be involved as well.

And the initial treatment of atrial fibrillation at that time was either intravenous heparin or enoxaparin. Of course, my job was to admit them and then what was done actually during the hospitalization and discharge was outside of my duty.

Q. Let me just ask, you don't intend to offer any testimony about your father's atrial fibrillation I take it.

A. No, I don't.

Q. In terms of your practice, have you ever prescribed warfarin?

A. During my work as a hospitalist, more often than not -- I can't say I've never prescribed warfarin, but usually when admitting a patient, you start them on heparin and see how they do, and then it's later, you know, it's later on when the warfarin gets prescribed. During internship and residency in Boston, I would have prescribed warfarin for

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patients during their hospital stay as a -- you know, during that medical training.

Q. Do you have any recollection of prescribing warfarin since your internship and residency?

A. There -- as I think about it, there probably were several cases as a medical hospitalist where I admitted the patient, started the IV heparin and then gave the first dose of Coumadin, and then with the instructions to test, you know, to draw PT/INR in the morning.

Q. Have you ever initiated prescriptions of warfarin?

A. No.

Q. Have you treated patients who suffered from strokes?

A. Yes.

Q. Have you been responsible for the care of patients on warfarin in terms of ongoing monitoring of those patients?

A. No.

MS. PRESBY: Objection, form.

Q. And you've never prescribed Pradaxa

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or any other novel oral anticoagulant?

A. No, I have not.

Q. That's just because of the timing of when they came on the market?

A. Correct.

Q. That was after your medical practice had ended?

A. That's correct.

Q. Did you ever read the Pradaxa label as kind of a practicing doctor?

MR. MOSKOW: Objection, form.

A. I read the Pradaxa label as a regulatory expert keeping up with all the various developments. Given the newness of this, you know, this class, I've read the label.

Q. When did you first read the label?

A. On the FDA website, so when it became available, so it would have been after approval and when it was posted on the FDA website.

Q. When you were at Sanofi?

A. When I was at Sanofi.

Q. You've never read it as a practicing doctor, the Pradaxa label?

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MR. MOSKOW: Objection to form.

A. The label would have been available after I stopped practicing, so the answer is no, I never read it as a practicing physician.

Q. You state on page 2 of your report that you've treated patients with anticoagulation therapy who have presented to the hospital with serious bleeds. Is that correct?

A. I've treated patients with serious bleeds and I've treated patients presenting to the hospital. I don't quite understand your question.

Q. Have you treated patients who have anticoagulant bleeds?

A. Yes, I have.

Q. And that's all warfarin bleeds; correct?

A. That would have been warfarin bleeds, it may have been some enoxaparin bleeds, and it may have also been sub Q heparin because part of the practice at the time was giving large doses of sub Q heparin. So heparin, sub Q IV, and enoxaparin.

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Q. Can you quantify how many times you've treated warfarin bleeds in your career?

A. During my gastroenterology fellowship, much of what we did on an emergency basis were GI bleeds, and many of those patients were on either aspirin or warfarin or some sort of anticoagulant. I wouldn't be able to quantify the number but, you know, there was a percentage of serious bleeds that were likely associated with warfarin.

Q. So let me see if I have that. When you were a gastroenterology -- and I always get these terms mixed up -- resident or fellow?

A. Fellow.

Q. Fellow. When you were a gastroenterology fellow, it was not uncommon to see warfarin GI bleeds. True?

A. Correct.

Q. And that's because warfarin has a well-known bleed profile generally and gastrointestinal bleed profile specifically?

MR. MOSKOW: Objection to form.

A. Correct.

Q. And you were not specializing in

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warfarin bleeds, you were specializing in gastroenterology issues, and part of specializing in gastroenterology issues is you're inevitably going to see a reasonable number of warfarin gastrointestinal bleeds; correct?

MR. MOSKOW: Objection, form.

A. That's correct.

Q. Just comes with the territory when you were practicing?

A. Correct.

Q. And those can be quite, quite serious bleeds; right?

MR. MOSKOW: Objection to form.

A. Yes.

Q. Since you've been a gastroenterology fellow, could you quantify in your medical practice how common it was for you to see warfarin bleeds?

A. It was not very common because I was a hospitalist, not an intensivist. And so if there was a serious GI bleed, that wouldn't have come to me, it would have gone to the intensivist. So there's a certain selection

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bias there.

Q. Got it. Your focus would not be on the serious warfarin GI bleeds; that would have gone to someone else at the hospital?

A. That's correct.

Q. Did you ever administer treatment to patients who had warfarin bleeds?

A. Yes.

Q. Did that include Vitamin K?

A. It included Vitamin K.

Q. You've heard of Vitamin K referred to as a, quote, reversal agent for warfarin; right?

A. Yes.

Q. In your experience how long does it take for Vitamin K to fully reverse a serious warfarin bleed?

A. Well, one of the concerns is there is variability, and it also has to do with how much Vitamin K you give. And over the years there has been a disagreement on whether to give a little or a lot, because if you give a lot, then it takes a long time to restart the Coumadin. There's also some question on

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whether or not giving a lot actually speeds up the effect.

And then for when I was in practice, we would often give fresh frozen plasma at the same time for a more immediate effect while the Vitamin K kicked in. So the thought was it would take a number of hours for Vitamin K, but sometimes you actually saw a quicker onset. But there was a lot of variability.

Q. It can take more than a day with Vitamin K; right?

A. It can -- there are -- I can think of examples when it took more than a day.

Q. Even with fresh frozen plasma, it can take hours and hours and hours; right?

MR. MOSKOW: Objection to form.

A. I had pretty good luck with fresh frozen plasma, so --

Q. How long?

A. Pardon?

Q. How long would fresh frozen plasma take?

A. Just an hour or two.

Q. Have you reviewed the data that's

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inconsistent with that on fresh frozen plasma and how long it takes?

A. I'm speaking about what I did back in the 1990s. There have been a lot of publications since then. And so my practice now would be -- might be different based upon data. But that was a snapshot in time.

Q. My question is simply have you reviewed the data from actual studies that exist on how long it takes Vitamin K to work, how long it takes fresh frozen plasma to work?

A. I have -- I have not done a systematic review and nor has that been something that I focused on for my report. I do know of articles where the time frame is actually longer than what my experience was.

Q. Okay. And you know that both Vitamin K and fresh frozen plasma carry their own independent risks?

A. Yes.

Q. What are some of the risks of fresh frozen plasma?

A. Well, in the days before HIV testing and hepatitis C testing, there was viral

transmission. And even today with Sika and some other viruses, if they're not specifically testing, any blood product can then transmit. And Vitamin K sometimes is an all-or-nothing; it can actually cause clotting.

Q. Have you ever used a -- Vitamin K can cause the very problem that you're taking warfarin to prevent, like a stroke?

A. That's correct.

Q. Have you ever used an anticoagulation test in your career -- in your practice?

A. Yes.

Q. And when was the last time you did that?

A. That would have been in 2010.

Q. Was that an INR test?

A. So it was an INR, a PT, PTT, INR.

Q. And that's what I was going to ask. Have you used the APTT test?

A. Yes, I have.

Q. Have you used the TT and the ECT test?

A. I have not, once again because they were not routinely available up until 2010.

Q. You had -- you were at the FDA from '95 to 2007; correct?

A. That's correct.

Q. Did you ever work on any atrial fibrillation treatment when you were at the FDA?

A. I was for a period of time in the cardiovascular devices division, and there were some devices at that time that dealt with atrial fibrillation. This was around the time of automatic defibrillators and things like that. So I did have experience -- regulatory experience on the device side with cardiovascular issues during that part of my career.

Q. What about in terms of anticoagulation? Did you have any experience with anticoagulation while you were at the FDA?

A. Yes, I did.

Q. And what was that experience?

A. That was when I first became GI division director. There was -- GI was combined with hematology at that time, and so all of the different hematology products,

including some of the anticoagulants, were there. Then during the reorganization they split hematology to go to the oncology office, and then GI was where I remained as a -- having trained in gastroenterology.

Q. So what anticoagulation products did you ever have responsibility for when you were at the FDA?

A. Well, I would have to look back to make sure that I wasn't giving away any proprietary or confidential information, because those would have been under IND review, and that's confidential information.

Q. Subject to a FOIA request, though; right?

A. For redacted, yeah.

Q. Are there any products on the market that you have worked on while you were at the FDA that are anticoagulation products?

A. Well, it would have been anything that was under IND back in 2005.

Q. Okay. Is there any such thing?

A. I would have to go back and check.

Q. You don't know, sitting here today,

of any anticoagulation products you've worked on while you were at the FDA that have ever been approved?

A. There are a number of products that never got approved, and I would have to look back and see if some of the ones that were subsequently approved were actually there during that time.

Q. Do you have any recollection of working on an anticoagulant product that was approved?

A. Like I said, I really am reluctant to give away anything that's -- one of the things we learn at FDA is that you don't talk about products in -- under IND. You know, companies who own the product can talk about development. But when I was at the FDA we were told you're not even supposed to reveal the existence of an IND, let alone how it's going.

Q. That's why I asked the question the way I did. Are you aware of any approved products that you worked on in terms of anticoagulation while you were at the FDA?

A. And I would have to think about that.

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Q. Can you identify any sitting here right now? Approved products for anticoagulation that you worked on while you were at the FDA?

A. No, I can't think of any right now.

Q. On page 3 of your report, Exhibit 1, you make reference to something that you just referenced now. "I did get to know" -- I'm in paragraph 13, second-to-last sentence: "I did get to know the medical officers and hematology team leaders during this time period and maintained professional contact over the years, understanding their analytic perspective during the regulatory review process for hematology products."

Why is that relevant to your opinions in this case?

A. Well, because many of the anticoagulants are reviewed in both the hematology division as well as the cardiorenal division, and there are a lot of interactions between the two, and even when there are no formal consults, some of the thinking from hematology worked its way into cardiorenal and

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vice versa.

Q. Do you know of any hematology role that has been played with respect to oral anticoagulants?

MR. MOSKOW: Objection to form.

A. Only what would be publicly available on the FDA website, but I -- offhand I don't know of any.

Q. Okay. You're not here to speak for the FDA; correct?

A. That's correct.

Q. In fact it would be unethical for you to purport to speak to the FDA; correct?

MR. MOSKOW: Objection to form.

A. I'm retired FDA and so I'm speaking on my experience from my time at FDA, but also then in industry.

Q. So come back to my question. It would be unethical for you to purport to speak for the FDA in this matter; correct?

MR. MOSKOW: Objection to form.

MS. PRESBY: Form.

Q. Do you know?

A. I guess I'm having trouble with the

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ethics.

Q. Okay.

A. Because it would be ill-advised and would be unwise.

Q. Would it be illegal?

MR. MOSKOW: Objection to form, calls for a legal conclusion.

A. I'm -- you know, I don't know -- I know when I left the FDA there were certain guidelines, ethics guidelines, and that wasn't one of them specifically. But I'm not an employee of the FDA now, and therefore I'm not speaking for the FDA now.

Q. Have you spoken with anyone at the FDA about this matter?

A. No, I have not.

Q. Do you keep in touch with people at the FDA?

A. Yes, I do.

Q. You've raised various concerns about both the FDA's work on Pradaxa and Boehringer's work on Pradaxa in your report; correct?

A. Yes, I have.

Q. Have you raised any of those concerns

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with former colleagues at the FDA or with anyone at the FDA?

A. Not since I've started working on this case.

Q. Have you done it before?

A. I had a ongoing dialogue with Bob Temple who I worked with a number of years ago.

Q. About Pradaxa?

A. Not specifically about Pradaxa, but about anticoagulation and bleeding. I had always felt that he minimized the severity of GI bleeding, and having trained in GI and having seen patients die from GI bleeds, you know, I would communicate that to him. And we also have had an ongoing dialogue about aspirin. He doesn't believe in primary prevention of aspirin, only secondary. So, you know, he and I have an ongoing dialogue but never have specifically talked about Pradaxa ever and not really had a dialogue since I've started on this case.

Q. Have you had any dialogue ever with anyone at the FDA about any -- I'm going to use the term NOAC, novel oral anticoagulant? Have

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you ever had any dialogue with anyone at the FDA, Dr. Temple or otherwise, about any novel oral anticoagulant or about novel oral anticoagulants generally?

A. I did comment to Dr. Temple that I liked his slides when he came out with them in 2014 and 2015, and I've referenced those slide sets in my report. But we didn't -- we didn't go into any depth.

Q. When did you make that comment to him? Around the time that he presented those slides?

A. It would have probably been either late 2015 or maybe after the holidays, January 2016.

Q. Okay. Now, at that time you were employed at Pfizer; correct?

A. 2015, '16 I was an independent consultant. I left Pfizer in April, March-April of 2015. So I was independent then.

Q. Do you -- you know what a citizen's petition letter is?

A. Yes, I do.

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Q. Do you have any -- you've not written a citizen's petition letter about Pradaxa?

A. I've not.

Q. Do you have any intention to do so?

A. No, I do not.

Q. You know that a citizen's petition is a vehicle that you or any other citizen has to write to the FDA and raise concerns including if you think a drug has inappropriate labeling; correct?

A. Yes, I do.

Q. And the FDA will act on citizen's petitions, it will review them and in many instances give a full decision --

MR. MOSKOW: Objection to form.

Q. -- as to whether it agrees or disagrees with the citizen's petition; correct?

A. That's correct. I had not thought about that until you mentioned that but that actually is a good idea, but.

Q. Do you have an intent to do so now?

A. No, I don't.

Q. If you did would you disclose the fact that you're a paid expert for the

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plaintiff lawyers?

A. Well, it's a theoretical because I really -- I don't plan to submit a citizen petition, and I would need to go back -- the FDA has guidance documents, and I would follow that, and any sort of disclosure that I would need to make I certainly would make.

Q. You would make that disclosure?

MS. PRESBY: Objection, form.

A. If the FDA guidance on submitting citizen's petition recommends that that disclosure is made -- and nowadays disclosures are a big part of publications and everything -- I would certainly be willing to do that, you know, to follow the rules and the guidelines.

Q. You mentioned disclosures are a big part of publications. You've never published on Pradaxa; correct?

A. That's correct.

Q. You've never published on any stroke prevention treatment; correct?

A. That's correct.

Q. You've never published on strokes at

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all or atrial fibrillation at all; correct?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. If you were to publish on Pradaxa, would you disclose that you're a paid plaintiffs' expert?

MS. PRESBY: Objection.

MR. MOSKOW: Objection to form, calls for speculation.

A. If I were, I would certainly disclose that.

Q. Okay. If you were to publish?

A. If I were to publish.

Q. Is there a reason that you would not write a citizen's petition letter to the FDA regarding your views in this case?

MR. MOSKOW: Objection to form.

A. Based upon my FDA experience, I don't necessarily think that citizens' petitions are that effective, and a lot of work goes into them, often with very little impact. And so I wouldn't see that as something that I would need to do. And it's often in the realm of -- many of the law firms do that, and whether or

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not they have utility doesn't seem to matter there.

Q. Do you have any intention -- strike that.

MR. SCHMIDT: Let me say for the record, I don't think simultaneous objections are proper. I don't want to have a big fight about it but I'm going to ask just one of you guys to object.

Q. Doctor --

MR. SCHMIDT: I'm not saying it's been disruptive; it hasn't. But I don't think it's proper and I wouldn't want it to be disruptive.

MS. PRESBY: It won't be disruptive. But I just for the record want to say I disagree based on our protocol.

Q. Doctor, have you expressed the views you've expressed in your report in any context outside of this litigation?

A. I have not.

Q. Has there been any way in which you have expressed your views on Pradaxa or on the

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FDA's regulation of Pradaxa other than in the context of being paid by plaintiffs' lawyers?

A. I have not.

Q. Do you have any intention to do so?

A. I don't.

Q. When you were at the FDA -- I'm going to ask you in a minute about your work at Sanofi and your work at Pfizer. When you were at the FDA did you work on any Sanofi or Pfizer drugs?

A. Yes, I did.

Q. Which ones?

A. So when I was at FDA in the GI division I worked on Protonix, which was a Wyeth drug which then became a Pfizer drug. That's a proton pump inhibitor. And there was a Sanofi Synthelabo drug that I'm blanking on the name but it was actually part of the FDA EMA joint review process. So we were on a videoconference with Sanofi and EMA as part of that development program.

And then of course Sanofi Synthelabo merged with Aventis to became Sanofi-Aventis who I work with. Those are the notable

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interactions.

Q. Did you work on any products that were later withdrawn from the market?

A. Not either for Sanofi or Pfizer.

Q. Okay. Did you work -- did you, in fact, approve a product called Bextra that Pfizer made?

A. Actually, I did not.

Q. Okay. Did you sign letters approving it?

A. I signed letter -- so as acting director of the analgesics division, I signed labeling supplements because it was well after the approval, and I was the lead negotiator on the FDA side to impose the black box on Bextra for Stevens-Johnson syndrome. So my signature would have been on that as well.

Q. And then you were at Pfizer when Bextra was pulled from the market; correct?

A. I was at FDA when Bextra was pulled from the market.

Q. When was Bextra pulled from the market?

A. It would have been in 2005, and I was

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still at FDA then.

Q. Were you at -- did you have any work on Bextra while you were at Pfizer?

A. I'm not aware of any work on Bextra because I was at Pfizer from January 2012 until early 2015. So I'm not aware of any development work on Bextra at that time.

Q. Okay. You left the FDA in 2007. What month did you leave?

A. It was in the March-April time frame.

Q. And you went straight to Sanofi?

A. And I left FDA because I was recruited by Sanofi to become their FDA liaison.

Q. Did they talk to you while you were at the FDA, while you were still employed by the FDA?

A. They -- I was contacted by a recruiter in February 2007. I notified my supervisor of that. I interviewed. And then part of the process was I recused myself from anything -- and there were no Sanofi-Aventis products. So I followed the procedures. And then I was offered a job and started I think

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late March, early April of 2007.

Q. And what made you switch?

MR. MOSKOW: Objection to form.

A. Well, the honest answer is that I'd been at FDA for 11 years, I was mid career, I was looking for more. It was an amazing opportunity to become the head FDA liaison for a major pharmaceutical company. And, you know, my children were, you know, nearing college age and it was time for a change, and I welcomed the opportunity to work with an international company and spend time in Paris and learn new things.

Q. What's the relevance of your kids nearing college age? I think I know the answers having kids of my own nearing college age, but --

A. It's very difficult to pay for college on a government salary.

Q. Did you value the work you were doing at a pharmaceutical company in terms of bringing new medicines to patients?

MS. PRESBY: Objection, form.

A. I enjoyed my work at Sanofi because I

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was able to bring my FDA insights to an organization that benefited from my experience. I was able to establish an office of FDA liaison and a process of interacting with FDA that's continued long after I left. And I think I also had an impact on some of the internal decisions of terminating programs where the benefit didn't outweigh the risk, as well as, you know, getting things approved.

So I think my expertise benefited Sanofi, and I learned quite a bit about the pharmaceutical industry making that move.

Q. Were you -- when you were at the FDA were you ever subject to any kind of public criticism for your work at the FDA?

MR. MOSKOW: Objection to form.

A. Yes, there was public criticism.

Q. And what was that?

A. That was during the Vioxx issue. I had been -- I was deputy office director, Office 5. And when Lee Simon, who was the analgesic rheumatology director, left FDA to go back to Harvard, they made me acting director. It's a routine practice at FDA that if you're

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at one level and somebody below you leaves, you have then a higher level person acting until that position could be filled.

And while I was in that acting director position, we got the phone call from Merck setting up the in-person meeting where they announced that they were withdrawing Vioxx. So I became the point person with the interactions with Merck. It was my job to interact with Ned Braunstein, who was head of regulatory, U.S. regulatory at Merck. And because of that position and my job of interacting in the withdrawal of Vioxx, as well as the planning of the 2005 February advisory committee meeting, my name came up in one of Senator Grassley's emails and -- and announcements. And because of that he requested an Inspector General investigation.

Q. Okay. So what was the specific criticism that was made against you?

A. The criticism from Senator Grassley's -- it was actually his staff I found out later -- was I was colluding with Merck. And it was after Vioxx had been withdrawn so it

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was always very confusing to me what I was colluding over. And the Inspector General investigation, which included a sworn deposition, found there was no basis for the, you know, that allegation that Senator Grassley's staff had made.

Q. So there was an Inspector General investigation of you?

A. Yes.

Q. And you gave testimony in that investigation?

A. Yes, I did.

Q. Do you have -- do you retain that testimony?

A. No. I was never given that sworn deposition.

Q. And was there a report written by the Inspector General?

A. I was never shown a report and I was told that Inspector General investigations are -- results are not made public, unlike GAO.

Q. So how were you told the results of it?

A. I was told by the investigator that

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there was no basis for the claim and the investigation had concluded and I was cleared.

Q. Okay.

A. And that was prior to Christmas of 2006.

Q. There was no document you were given on that or anything?

A. No, I wasn't.

Q. And do you recall that the allegation related to one of your colleagues and an accusation that you were undermining one of your colleagues at the FDA?

A. Oh, the -- and it's still -- if you do a Google search, it's all still there. The allegation was that I was colluding against David Graham, Dr. Graham, who was a safety officer.

Q. He's a pretty well-known safety officer at the FDA?

A. He's very well known. He's been critical of many, many drugs over the years.

Q. I was going to say, he's someone who's pretty ready when he sees a safety issue to say this drug should be pulled from the

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market?

A. Yes, he has said that for many drugs.

Q. That's what I was going to say. There's been a number of instances where Dr. Graham has publicly or within the halls of the FDA said this drug's too dangerous, we need to take it off the market?

MR. MOSKOW: Object to the form.

A. That's what he has said.

Q. He's known as a bit of a gadfly within the FDA?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. Well, you know, of course I never worked with him directly because I was in new drugs, he was in drug safety. We were in different silos. And so neither one of us really crossed paths and neither one of us had any direct oversight of the other. So I'm certainly aware of what he did and read extensively in the press.

Q. I was being jokey. Let me ask it a little more seriously.

Do you have a good regard for

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Dr. Graham and his safety efforts at the FDA?

A. The honest answer is that there are many drugs that he criticized where he was wrong, that the safety, the benefits did outweigh the risks, and there were a few examples where he is right. And if all drugs are bad, eventually you're going to be right. And so his tendency is to see the negative, and there have been a few times he's been correct, but there are many drugs that are still being used today with good benefit/risk where he felt they should have been withdrawn and that actually probably would not have been a good thing.

Q. So, but fair to say from what you just said, and I think I'm quoting what you just said, you think Dr. Graham has a tendency to see the negative in drugs?

A. Well, his role at FDA was in drug safety. My role was in premarket approval. And so he had a role to play and he played that role.

Q. But in that role, I think you said a moment ago his tendency was to see the negative

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in drugs.

A. If you do a Google search, you see that he's criticized many drugs, as you probably did to find my, you know, my experience.

Q. So what I said is correct?

A. His tendency was to be negative, that's correct.

Q. Okay. When you were at either Sanofi or Pfizer did you recuse yourself from any FDA interactions?

A. Well, under the policy I was given, the ethics policy, I could have no direct interactions with FDA for the first year, when I was at Sanofi. And if I was directly involved or had approved something -- you know, if I was directly involved, then it was two years, and if I was actually the signatory authority of approval, there was some wording for actually a lifetime ban of interacting. So I followed those rules to the letter.

Q. What did you -- what made you leave Sanofi and go to Pfizer in 2012?

A. Well, I was contacted by a recruiter

for a position of VP U.S. regulatory strategy, which was a step up from -- I was VP U.S. regulatory policy, and so in order -- and the opportunity to be the top regulatory person in the U.S. for Pfizer was an amazing opportunity. And so I interviewed and I got the job and was quite glad I did because the experience I got in working with a high-quality organization like Pfizer, working in the advertising and promotional space, it really broadened my perspective even further.

Q. Did you work on any medicines at either Pfizer or Sanofi that were subject to litigation?

A. Well, it seems like all medicines are subject to some sort of litigation nowadays.

Q. Yes, it does.

A. So when I was at Pfizer I was involved with the approval of Xeljanz, which is the first JAK inhibitor. I don't know what current litigation there is but I'm sure there's something. Duavive, which is an estrogen combination, involved in that approval. I worked with the vaccine folks on

Trumenba, which is a meningococcal B vaccination. And I also worked with the oncology group for palbociclib, which became Ibrance, which is one of the first breakthrough designation drugs, and that got approved -- accelerated approval and then full approval.

Q. Were you ever deposed?

A. I was never deposed at Pfizer.

Q. Or at Sanofi?

A. Or at Sanofi.

Q. Now, at Pfizer I think you say in your report that you were -- in your CV that you were the lead for U.S. regulatory strategy across all Pfizer business units. Is that correct?

A. Yes. So I worked in parallel with the regulatory leads of the various business units.

Q. Were you responsible ultimately for every -- I think you say in your report, I was the final signatory on all labels that were sent to the U.S. FDA. Is that correct?

A. As VP U.S. regulatory strategy at Pfizer, that's correct.

Q. And would that include products that you had a co-promote relationship with another company? Would you still have a role on the labeling?

A. Actually, not.

Q. Okay.

A. Because in the co-promotes, they always had someone who was the U.S. lead, and if Pfizer was the U.S. lead, then I would have. But in many cases, the U.S. lead was the other company, and therefore, their regulatory person would have had the sign-off.

Q. So Eliquis is a Pfizer drug; correct?

A. Eliquis is part of the Pfizer Bristol-Myers Squibb partnership, and Bristol-Myers Squibb holds the U.S. NDA, which means the Bristol-Myers Squibb regulatory person was the signatory authority.

Q. Pfizer profits off of Eliquis sales; correct?

MS. PRESBY: Objection, form.

A. There is a partnership and I'm not aware of what the interaction is. But since there is a partnership, they have -- they

shared in the costs and I'm sure there's, you know, the business -- there's a business arrangement but I don't know the contract.

Q. Does Pfizer have any role in the labeling for Eliquis?

A. I was not involved in that because Bristol-Myers Squibb was the lead on that NDA approval.

Q. So as far as you know did anyone in regulatory at Pfizer have any role regarding Eliquis?

A. I know there were some individuals in advertising and promotion who had an advisory role, and there would have been some in regulatory that maybe had an advisory role, but not being directly involved with it, I don't know who had authority since the ultimate sign-off was Bristol-Myers Squibb.

Q. Eliquis was launched when you were at Pfizer; correct?

MR. MOSKOW: Objection to form.

A. Yes, I was there.

Q. And it was on the market for several years while you were at Pfizer; correct?

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A. I didn't follow it that closely but it was approved and then, like I said, I left early on in 2015, so it would have been on for --

Q. Two years? Correct?

A. I will -- I will take your word for that.

Q. Did you have any role or any discussions regarding Eliquis?

A. Eliquis was discussed in general at some of the meetings, the regulatory meetings as general issues in process. You know, there always were discussions about how to interact with a partner. But as far as, you know, the data and the nuts and bolts application, I was not part of those discussions.

Q. So you were responsible ultimately for all Pfizer labels; correct?

A. That's correct.

Q. Did you have the ability, whether it was binding or not -- strike that.

Who was your counterpart at BMS who would have had that role as to Eliquis?

A. I'm not sure.

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Q. You don't even know?

A. I know Dr. Hukkelhoven was at BMS. He was the head of regulatory. But I think he might have -- I think he's a senior VP so he's not -- I was a VP. So I don't know who exactly under him would have been involved.

Q. Did you have the ability if you wanted to raise concerns -- strike that.

You talked about advisory work that people on your team would have done regarding Eliquis, including on promotional issues; correct?

MR. MOSKOW: Objection to form, mischaracterizes the testimony.

A. There were people in Pfizer advertising and promotion who were on some of the various advisory groups for Bristol-Myers Squibb.

Q. And were those people under your supervision?

A. There were some that were under my supervision.

Q. So people on your team were giving advice on the promotion of Eliquis; correct?

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MR. MOSKOW: Objection to form.

A. Yes.

Q. And you understand it's a basic rule when you're promoting a medicine that the promotion has to be consistent with the label.

A. I'm aware of that, yes.

Q. And if the label is defective in some core way, then the promotion will correspondingly be defective; correct?

A. Are we talking in general or --

Q. Yes.

A. In general, that's correct.

Q. Was it important to you that when your team members were working on a product, whether it was Eliquis or something else, that they acted consistent with patient safety?

A. That's important, yes.

Q. Would you expect them to raise issues or concerns they had with you if what was being done was inconsistent with patient safety?

MR. MOSKOW: Objection to form.

A. Well, I would expect them to raise the issues, but I would not have been the appropriate person to raise the issues with,

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given that it was a partnership with Bristol-Myers Squibb. I had a lot on my plate for all the Pfizer products, and so their input or any input they may have given on these advisory committees would have gone to Bristol-Myers Squibb and not to me.

Q. If they had a concern about the disclosures that were being made regarding Eliquis, would you expect them to raise them with you, if they were concerned that the disclosures were jeopardizing patient safety woman.wouldn't.

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. I wouldn't have expected that they would have raised them with me; I would have expected that they would have raised them with the appropriate individuals on the committee, given that Bristol-Myers Squibb held the NDA.

Q. Did you have a vehicle to raise concerns you might have had about Eliquis with either people at Pfizer or your partner at Bristol-Myers Squibb?

MR. MOSKOW: Objection to form.

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A. It wasn't part of my duties to do that. And like I said, I had so much to do that was my responsibility that I didn't go looking for additional work. And I wasn't in that chain of command for Eliquis and I wasn't given the information, so I had -- I would have had no direct information to react to.

Q. Do you have any current relationship with Pfizer or with Sanofi?

A. Yes.

Q. And what are those relationships?

A. Well, the relationship with Pfizer is, you know, I'm an independent consultant and I am on the list at Pfizer as a vetted consultant contractor. And so if certain projects arise, I've been hired by Pfizer to advise.

Q. Okay. Do you have kind of an ongoing stream of work with them? I understand it's different projects but does it end up being an ongoing stream of work?

A. It's -- I've done -- you know, it's when the projects come available. So I don't know when the next one's going to be. But it's

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an episodic sort of thing. But I'm still on the contractor list.

Q. Okay. So let me see if I have this. Pfizer has a special list of contractors, approved contractors they use on consulting projects, and you're on that list?

A. Yes.

Q. And do you end up working with Pfizer every year?

MR. MOSKOW: Objection, form.

A. I worked with them last year and I worked with them this year.

Q. Okay. I'll take that as a yes.

A. Yes.

Q. Do you have a sense of your earnings from Pfizer every year?

MR. MOSKOW: Objection to form.

A. I know I've worked on three projects and I know what I've earned on the three projects and the cumulative amount on those three projects is less than 50,000.

Q. Do you anticipate working with them on an ongoing basis in the future?

A. I hope to.

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Q. Do you have any kind of stock or ownership in either Pfizer or Sanofi?

A. I do have stock with Pfizer because that's part of my retirement program, as well as part of my severance program.

Q. And you understand that the performance of that stock that you own is influenced by how Pfizer does as a company?

A. That's correct.

Q. You understand that Eliquis is one of the Pfizer blockbusters?

MR. MOSKOW: Objection to form.

A. I have never seen a good definition of "blockbuster." I know it's done well in the market, and obviously there's some incremental impact on Pfizer.

Q. I've heard some of your colleagues across the table refer to a blockbuster as something that makes more than a billion dollars a year. Does Eliquis fit that definition?

A. Based upon public information I've seen, yes.

Q. Are you aware of -- okay. And

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obviously how Eliquis does affects how Pfizer does, in part?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. Does that create in your view -- do you have any other ongoing relationship with Pfizer?

A. No.

Q. Do you have any other -- you don't have any pension or anything like that?

A. There was no pension but I do have Pfizer stock in my retirement account.

Q. That's what you just talked about; right?

A. Well, that and the severance.

Q. Okay. Are the severance payments ongoing?

A. The severance payments were completed in 2015, and I -- and then the vested stock that -- you know, so the stock awards that had been vested have come due on a periodic basis.

Q. Okay. Did you sign any kind of -- in connection with your severance agreement, did you sign any kind of disparagement agreement

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with Pfizer?

A. A nondisparage agreement, yes.

Q. That's a better way to put it. You'd have some legal problems if you signed a disparagement agreement. Would that nondisparagement agreement keep you from serving as an expert witness in an Eliquis case?

MR. MOSKOW: Objection to form.

A. I would -- I would have to -- I mean I would check with Pfizer on that and get a legal opinion before I did that.

Q. You're aware that there's -- just as there's litigation over Pradaxa, there's litigation over the other novel oral anticoagulants, Xarelto and Eliquis?

A. I wasn't aware of the Eliquis. I've heard about Xarelto.

Q. There is -- I'll represent to you there is Eliquis litigation that is ongoing. So I have it, if you were approached by Mr. Moskow or by anyone else about being an expert witness in Eliquis litigation, before you would do that, before you could do that,

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you would go back to Pfizer and say is this permissible?

A. Yes, I would. And I would think carefully about it, just having been involved with this case.

Q. What do you mean by that?

A. Well, I would just want to make sure that nothing I did in this case would have any negative impact on any future case.

Q. Okay. You understand that some of the criticisms you make in this case have been made against other oral anticoagulants; correct?

A. Well, that was not the focus of my study. And I'm not -- I'm not aware of that literature because that was not the basis of my report. So I've not heard about the same criticisms for Eliquis that I've heard for Pradaxa.

Q. You haven't seen some of the very same documents you've looked at where they talk about whether there should be monitoring for Pradaxa, they talk about whether there should be monitoring for Xarelto and Eliquis?

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A. I've seen those mentioned in the -- those articles, but those have not been the focus of my research.

Q. Do you know of any difference between how Xarelto works and how Eliquis works that would make blood concentration testing appropriate for Pradaxa but not for Xarelto and Eliquis?

MS. PRESBY: Objection to form.

MR. MOSKOW: Objection to form.

A. I'm not here to serve as an expert on Eliquis. There's a different mechanism of action, whether it be a direct thrombin inhibitor versus, you know, a factor 10. So there's a different mechanism of action. Pradaxa's the only direct thrombin inhibitor that I know of, and it's the one that I've studied. So I would actually like to just confine my analysis to that because that was the topic of my report.

Q. Well, you've seen Dr. Temple talk about whether there should be monitoring for Eliquis; right?

A. Only the slides that I referenced, he

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was talking about this new generation in general.

Q. Right.

A. So that would have covered all of them. He did specifically show a chart of risk of bleeding going up and benefit, you know, marginal benefit going down, and that was Pradaxa-specific.

Q. Do you know why that was Pradaxa-specific?

A. Because that was from the Reilly paper.

Q. Right.

A. Figure 2.

Q. Do you know that Boehringer undertook the effort in their pivotal trial to gather blood concentration data that neither the manufacturers of Eliquis nor the manufacturers of Xarelto did?

MR. MOSKOW: Objection to form.

A. Like I said, I did not do an in-depth analysis of the other anticoagulants.

Q. Do you know if what he said is true?

A. I do know out of the -- there were,

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what, 3,300 patients that didn't get tested but some did get tested, so it wasn't all patients in RE-LY who got drug levels.

Q. Can you answer my question, though? Do you know if there was drug level testing in the pivotal studies for Xarelto or for Eliquis?

MS. PRESBY: Objection.

A. I don't know that information.

Q. And do you have any basis sitting here right now to say that Xarelto and Eliquis are different in terms of whether they require some form of blood concentration testing than Pradaxa?

MS. PRESBY: Objection.

MR. MOSKOW: Objection to form.

A. I'm not here to opine on the other products.

Q. I understand your position on that. My question is do you know of any differences between them that makes blood concentration testing appropriate for Pradaxa but not for Xarelto and Eliquis?

MS. PRESBY: Objection.

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MR. MOSKOW: Objection to form.

A. I know that there's a different mechanism of action, those being factor 10 and this being a direct thrombin inhibitor. And so I would have to go through and see how a different mechanism of action might play a role in benefit/risk. My focus has been on this direct thrombin inhibitor and the need for testing for dose adjustment.

Q. That's why I asked my question the way I did. You can't tell me that the different mechanism of action makes blood concentration testing appropriate for Pradaxa but not for Xarelto and Eliquis; right?

MR. MOSKOW: Objection, form.

A. I can't tell you that; that's correct.

Q. So my question is is there anything you can tell me that you know that makes Xarelto and Eliquis different from Pradaxa that would make concentration testing appropriate for Pradaxa but not for them?

MR. MOSKOW: Objection to form, asked and answered.

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A. The different mechanism of action, you know, the way that you can test for Pradaxa, direct thrombin inhibitor, you know, the TT test, I don't know the performance characteristics of that with the factor 10 products because I didn't analyze those, I didn't study those and didn't look through their literature.

Q. Let me try it this way. You have seen discussion of those products in this broader discussion that has occurred over the past several years about whether blood concentration would be beneficial, such as with Dr. Temple, such as with the CRSC; correct?

A. Yes.

Q. Do you have any basis to rule out that there should be blood concentration for -- testing for Xarelto or for Eliquis?

A. I have no basis to rule in and rule out since that wasn't the focus of my report.

Q. And if I were to ask you to look at the data, such as it is, for Eliquis, and try to tell me whether your opinions on Pradaxa apply to Eliquis equally, would you need to

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talk to Pfizer first before you could go on record and give an opinion on that?

MR. MOSKOW: Objection to form.

A. I think I would talk to Pfizer to make sure I wasn't violating any agreement.

Q. Okay.

A. But in theory, I certainly could analyze any data set I was given.

Q. Okay. If you were to -- you understand that Eliquis and Pradaxa compete; correct?

A. I understand the U.S. market and that practitioners have various options, and so there is competition amongst those.

Q. To some extent every Pradaxa prescription takes money potentially away from Eliquis; correct?

MS. PRESBY: Objection.

MR. MOSKOW: Objection to form.

A. Well, I'm not here as an economist.

Q. I'm just asking as a regular person who has basic knowledge.

A. Yeah, well, I mean, part of what we -- you know, I have been reading is that

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there is an underutilization. There are patients who are not receiving anything now. And if you can provide a safer option, you actually can increase the size of the pie. So not every prescription of one takes away from the other if you have more patients in a underserved area getting treated. So a prescription for one doesn't take away from the other if you're increasing utilization in a beneficial way.

Q. You sound like some of our politicians in tax cuts.

MS. PRESBY: Objection. Seriously.

Q. Do -- are Pradaxa -- are Pradaxa and -- I'll withdraw that. I was joking.

Are Pradaxa and Eliquis prescribed to the same patients?

MR. MOSKOW: Objection to form.

Q. Do they have a very large overlapping patient pool?

MR. MOSKOW: Objection.

A. Based upon the U.S. label, there are some patients who would be appropriate for one who would be appropriate for the other.

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Q. Okay. Do you think it's any form of a potential conflict of interest to give testimony on Pradaxa when you have a financial interest with Pfizer?

MR. MOSKOW: Objection to form.

A. No, I don't.

Q. Okay. So if you were, for example, to publish a article on Pradaxa that was critical of Pradaxa, consistent with your report, would you make any kind of conflict of interest disclosure regarding your former or current work with Pfizer?

MR. MOSKOW: Objection to form.

A. I don't plan to publish, but if I did I would follow the appropriate disclosure rules, which would be to reveal that.

Q. You would reveal that?

A. I would reveal that.

Q. Okay. As a potential conflict of interest?

MR. MOSKOW: Objection to form.

A. Yes, for transparency.

Q. When -- when you were at companies, I take it you -- Sanofi and Pfizer, I take it you

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oversaw submissions that were made to the FDA.

A. That's correct.

Q. Did you have a practice of telling the scientists at your company that as they debated things internally -- let me take a step back. You understand that at pharmaceutical companies scientists will debate various issues about the safety of their medicines or about how they work; right?

A. Yes.

Q. They'll debate them by email or by memo or by meeting or however the case may be; correct?

A. Yes, I'm aware of that.

Q. And one thing companies will try to do is take that debate and from that debate develop a final position that the company thinks is right?

A. That's standard, yes.

Q. And that position might reflect everyone ultimately coming to agreement, it might reflect some people being kind of dissenting votes, so to speak; correct?

A. That's all within the realm of

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possibility, yes.

Q. When you were at a pharmaceutical company, did you make a practice of telling your scientists that as they had these debates you needed to be submitting any memos they wrote or emails they wrote as part of this debate to the FDA?

MR. MOSKOW: Objection to form.

A. That -- if you could clarify that, because I'm trying to understand what mechanism would be used to submit that to FDA if it wasn't part of an application or an IND.

Q. Well, for example, were you ever involved with discussing safety issues with the FDA?

A. Yes.

Q. And I take it those discussions of safety issues would reflect a good bit of discussion back at the company among your scientists as they tried to understand the safety issue and analyze it.

MR. MOSKOW: Objection to form.

A. Yes.

Q. Would you submit all the discussions

HARVEY

that the scientists would have on that safety issue to the FDA, whether it was emails or memos? Or would you try to come up with a final company view and submit that to the FDA?

A. Well, I would come up with a company view that would make sure it encompassed the broader discussion.

Q. Okay.

A. Yes. So I would submit the broader company view.

Q. Would you submit every precursor discussion to that company view?

A. No.

Q. Why not?

A. Given the many emails -- and I know where you're going with this, but given the vast number of emails and communications, that's not something you would submit to FDA because FDA -- you know, when you -- if you truly wish to communicate information to FDA, you want it to be clear and concise. You don't want to do what is referred to as a data dump because by giving thousands and thousands of patients, they may miss something, and by

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having a summary that covers the various points, if it's done accurately, then that encompasses the internal discussion and you don't have to submit everything, because by submitting everything, that doesn't necessarily increase the clarity, it just dilutes out those things that are most important.

Q. You would try to submit your best final view, integrating the views of the scientists?

A. That's what I would have done, yes.

Q. And that's what you understand to be appropriate in terms of what the FDA wants?

MR. MOSKOW: Objection to form.

A. That's what they'd expect from a reasonable company.

MR. MOSKOW: Let me ask that -- I'll let you finish the line of questioning, but next break.

MR. SCHMIDT: Sure. I'm almost done with this line.

Q. There would be times I take it where your scientists at your company would run various analyses on issues related to the

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safety or the efficacy of your medicines; right?

A. Yes.

Q. And some you might not even hear about; right?

MS. PRESBY: Objection.

MR. MOSKOW: Form.

A. Yeah, I can't say I heard everything that went on in the entire 100,000-person company of Pfizer.

Q. I thought that was an easy one. You didn't have a practice of submitting every analysis that scientists at your company performed to the FDA, did you?

A. I wouldn't have submitted every analysis, but significant analyses that I felt had an impact would get submitted through various mechanisms, either, you know, where appropriate, either under the IND or in annual reports. You know, there are different ways to submit it. And then FDA has that information. So if I felt it was significant, it would get submitted. And so based upon information I was given.

HARVEY

Q. So if you thought an analysis, I think the words you used were significant and had an impact, then you would submit it?

A. Correct.

Q. But not every other analysis?

MR. MOSKOW: Objection to form.

Q. If it was not significant and did not have an impact, you would not necessarily submit it; correct?

A. That would be -- not everything was submitted, so yes, correct.

MR. SCHMIDT: Why don't we take a break?

MR. MOSKOW: Thank you.

THE VIDEOGRAPHER: We're off the record at 10:11.

(Recess taken.)

THE VIDEOGRAPHER: Here begins media number 2 in the video recorded deposition of Dr. Brian Harvey. We're back on the record at 10:27.

BY MR. SCHMIDT:

Q. I'm just going to round out some questions about your background with what I

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hope is a speed round. You're not a cardiologist; correct?

A. I'm not a cardiologist.

Q. You're not a hematologist?

A. I'm not a hematologist.

Q. You're not a nephrologist or an expert in nephrology?

A. That's correct.

Q. You're not a geriatrician or an expert in geriatric treatment?

A. That's correct.

Q. You're not an epidemiologist?

A. I'm not an epidemiologist.

Q. You've no specialized training or education in epidemiology?

A. That's correct.

Q. You're not a pharmacologist?

A. I'm not a pharmacologist.

Q. You're not a pharmacokineticist?

A. I'm not a pharmacokineticist.

Q. Do you have any special training in pharmacokinetics?

A. Yes, I do. I have had training during my Ph.D. in biochemistry, which I got

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before going to medical school. I had training as part of medical school and as a fellow at Hopkins, I've availed myself of courses they had there. And then FDA had a very extensive internal training program and took all of those that I could from some, you know, of the well-known folks who were there and others while at FDA.

Q. Have you ever personally performed any pharmacokinetic or pharmacodynamic modeling?

A. I have not.

Q. Have you ever designed or overseen a clinical trial?

A. I have designed clinical trials. I've not overseen clinical trials.

Q. What's the largest clinical trial you have designed?

A. A 24,000-patient trial.

Q. Which --

A. I helped design the PRECISION trial when I was at FDA, which was Celebrex and Pfizer, to look at cardiovascular risk.

Q. What was the outcome of that trial?

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A. The outcome of that trial was actually made public about a year or so ago. The initial estimate was that it was going to be 20,000 patients based upon an expected event rate, and the event rate was lower than expected. So 24,000 patients or so were enrolled, and it came out that there wasn't an elevated cardiovascular risk for Celebrex over what they had previously reported.

Q. Celebrex of course is a Pfizer product?

A. Celebrex is a Pfizer product and is still on the U.S. market.

Q. Did you do any work on Celebrex when you were at Pfizer?

A. I was there when they were discussing the pending results for the PRECISION trial, and I'm trying to remember if the results got released when I was still at Pfizer or soon after.

Q. Did you have any FDA interactions regarding Celebrex when you were at Pfizer?

A. No, I didn't. Because the trial was ongoing and there was nothing to be done other

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than to wait for the data.

Q. Do you consider yourself an expert in assays?

A. Five years of my time at FDA were in the Center for Devices and part of that time was in the in vitro diagnostic group. I was involved with the approval of the hepatitis C PCR, RNA test, the Roche tests, and at my time there, I learned about in vitro diagnostic FDA regulation.

I'm not sure what makes one an expert but it's something that I've continued to follow and part of my consulting work is with in vitro diagnostic companies and policy.

Q. Have you ever been involved in development efforts for an assay?

A. I've been involved with the regulatory aspects of developing assays.

Q. What about the actual scientific aspects of developing assays?

A. No, I've not.

Q. And you say in your report you're not an expert on pharmaceutical regulation outside the U.S.; correct?

HARVEY

A. I'm not an expert outside the U.S. but have experience outside.

Q. You're not an attorney or a legal expert?

A. I am not.

Q. And you're not an expert on ethics?

A. That's correct.

Q. And I think you say in your report you're not giving an opinion as to whether Boehringer met state law standards or violated state law standards; correct?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. Are you offering an opinion as to whether Boehringer violated federal law standards?

MR. MOSKOW: Objection to form.

A. Can you just clarify? Because I'm --

Q. Do you have an opinion that Boehringer violated FDA standards?

A. FDA standards, yes.

Q. What were the violations?

A. Well, specifically the -- you know, a reasonable pharmaceutical company has a duty to

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report information that has an impact on benefit/risk. If I remember correctly, it's 21 CFR 314.70, often quoted by people from FDA. And that's where, when there's new information that becomes available, or new analyses of previous data, then the sponsor should be sending that to FDA and that should then be part of the label to help inform prescribers.

Q. Okay. So you believe there's a violation in terms of Boehringer failing to report information that was required by law to report to the FDA. Is that right?

A. I'm a regulatory expert so I base it upon the regulations, not upon the law, so I'm always very careful to confine it to a regulatory perspective.

Q. You understand regulations are law; right?

A. Regulations are promulgated by an agency based upon the law.

Q. Okay. Do you understand them to be legally binding on companies? Yes or no?

A. I understand -- yes.

Q. Okay. So do you have an opinion that

HARVEY

Boehringer violated FDA regulations requiring it to report information that it failed to report?

A. Yes.

Q. Do you have any other opinions about whether Boehringer violated FDA regulations or standards?

MR. MOSKOW: Objection to form.

A. Yes, I do.

Q. What are those opinions?

A. So as, you know, information became available and, you know, and I can go through point by point and it was outlined in my -- actually, may I open my report?

Q. Yeah. Just so my question's precise, I don't want to go through every single basis; I'm just asking you what were the violations in your view. One is failing to report information. What other violations, if any, do you believe that Boehringer made, federal regulations or federal standards?

A. So the information that was provided to FDA did not allow for the launch label to adequately inform prescribers, and subsequent

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information provided has not generated U.S. labels that adequately inform prescribers. And FDA has provided a roadmap of what to do in order for the sponsor to provide adequate information to improve the label, and that has not yet been done.

Q. So it's your opinion that they failed to provide adequate information and that that's resulted in a defective label?

A. An inadequate label.

Q. Are there any other violations in your view, other than failing to provide information resulting in what you believe to be an inadequate label?

A. Well, I'm reluctant to call it a violation, but --

Q. I'm just focused on violations.

A. Okay.

Q. I'll ask you about your other --

A. Can you define violation for me then?

Q. Some kind of legal obligation, whether it's in a statute or in a regulation, that you believe Boehringer violated in its interactions with the FDA regarding Pradaxa.

HARVEY

A. So I don't believe that they provided adequate information on the various subpopulations that were at higher risk in order to provide adequate benefit/risk for those subpopulations.

Q. I'm going to stop you there because I think you've covered failure to provide information. I'm asking if there's any other categories of violations. I'll come back to failure to provide information.

A. Well, you know, there was research done based upon my review of the documents on a reversal agent. That was well before the submission of the NDA and yet that doesn't appear to be actively pursued. And given what we know about anticoagulation, the development and approval of a reversal agent would have improved the benefit/risk profile of this product.

Q. Is it your opinion that Boehringer violated a federal law or regulation in the manner in which it developed the reversal agent?

A. That's why I asked for a

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clarification on what you thought was a violation.

Q. Right. I gave you that clarification. Tell me in your opinion, did FDA -- I'm sorry, did Boehringer violate any federal regulation or any federal law? Yes or no.

A. No.

Q. But you do have concerns about how Boehringer acted?

A. I believe that a reasonable pharmaceutical company, if they had the information regarding a reversal agent, would have developed that in parallel with the agent.

Q. Now, in terms of submission of information -- in terms of submission of information, have you identified any specific information, data that Boehringer had that was required by regulation or statute to submit to the FDA but failed to submit to the FDA?

A. I believe that the modeling data was significant information that should have been submitted to FDA and it would have fallen under 21 CFR 314.70.

HARVEY

Q. So did -- just to be sure I understand your testimony, did that regulation you just cite impose a legal obligation on Boehringer to submit its modeling information?

A. I'm -- I'm a regulatory expert, not a lawyer, so we don't normally think of things in that term. I think a reasonable company --

Q. Let me rephrase it then. I'll withdraw it and rephrase it. Did Boehringer have an obligation -- I'm not asking about reasonable companies, I'm asking about an obligation. Did Boehringer have an obligation under federal law or federal regulations to submit its modeling data? Yes or no?

MR. MOSKOW: Objection to form.

Q. Or I don't know.

A. The practice -- the regulatory practice in the U.S. is based upon the regulation but also industry standards.

Q. I'll ask you about industry standards. I'm just focused now on the regulation. Did Boehringer have an obligation under any regulation or statute you know of to submit the modeling data to the FDA?

HARVEY

MS. PRESBY: Object to form.

A. As a regulatory person it's my understanding that the significance of the modeling data, it should have been submitted to FDA for their review, and it should have been singled out as important information for FDA to see at the time it was first generated.

Q. And failure to do that was a violation of the regulation in your opinion?

A. Like I said, I'm uncomfortable to say it's a violation of specific regulation, because that's not how we operated when we were at FDA.

Q. Did the FDA ever have access to that modeling information?

A. It's my understanding that later, that some of that modeling was used as part of the pediatric development. But not at the time that it was first generated.

Q. Let me ask you this question. Is there any information you know of that you believe should have been submitted to the FDA regarding Pradaxa but that as we sit here right now today has not been submitted to the FDA

HARVEY

regarding Pradaxa?

MR. MOSKOW: Objection to form.

A. Well, I would have to go back and look, because there was some information that was available at the time of NDA submission and some that was available soon after that wasn't submitted, and then at a later date, it was submitted as a larger data dump. And then there have been publications that have come out, 2014, '15, '17. But some of that data in even the most recent publications was available back at the time of initial NDA.

So yes, some of the information has been shared with FDA, but in some cases it's up to a five-year or more time delay, which doesn't seem to make sense from a regulatory perspective.

Q. Come back to my question then, please. My question is really simple. As we sit here today, can you point me to any information that should have been submitted but as of today has not been submitted to the FDA?

MR. MOSKOW: Objection to form, asked and answered.

HARVEY

A. As of today, no, I can't point to anything specifically.

Q. Can you point me to -- you raised a timing concern about when information was submitted. Can you point me to any information that you believe -- strike that. Let me focus my question.

We have been talking about modeling information; correct?

A. Correct.

Q. That's data -- it's not data. It's attempts to take data on plasma concentration and make predictions based on that data; correct?

A. That's not correct.

Q. Okay. Which part of that is not correct? Strike that.

Is the modeling data based on plasma -- is the modeling based on plasma concentration data?

A. That's my understanding.

Q. And is it an attempt to make predictions about outcomes if you try to adjust dose such that you adjust plasma concentration?

HARVEY

A. That's one of the intended outcomes of using modeling.

Q. The modeling data that you believe was required or should have been submitted, you have seen it submitted; correct? You are aware that it has been submitted?

A. Ultimately, it was.

Q. And can you point me to any action -- and you know it's been publicly discussed; right?

A. Correct.

Q. And it's been published on, as you noted; right?

A. Uh-huh.

Q. Correct?

A. That's my understanding.

Q. And there have been special workshops to talk about it; right?

A. Yes.

MR. MOSKOW: Objection.

Q. There's even been some discussion in the lay media about it; right?

A. I'm not aware of the lay media but that wasn't really the focus of my report.

HARVEY

Q. Fair point. Here's my question. Can you point me to any specific action that the FDA has taken in response to modeling data on Pradaxa as it's learned about that data or that analysis?

MR. MOSKOW: Objection to form.

A. Well, once again, the concern is about the delay. You know, the -- the utility of the modeling data, that would have been good to have during the initial NDA review and the immediate aftermath when there was the reporting of adverse events, including significant bleeds. Now, a number of years after the fact, when the company was faced with the requirement to do pediatric studies, the modeling then appeared to have utility with helping design those pediatric studies.

And so I don't know what's been submitted to FDA because having a publication or a workshop is not an FDA submission for NDA supplement or labeling change.

Q. Have you reviewed the NDA to see if the modeling information has been submitted as part of the NDA?

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A. I did not see the modeling information in my review of the initial NDA approval.

Q. No, I'm talking the NDA as it exists today.

A. I have not -- I have not reviewed every generation of what's been submitted. I mean, the NDA is that initial submission, so let's clarify -- and then supplemental NDAs. I'm not aware that FDA has received that modeling data as a submission of an sNDA in order to get that information in the label. I'm unaware of that.

Q. Have you reviewed the regulatory correspondence in full between Boehringer and the FDA to see whether and how Boehringer has submitted modeling information to the FDA?

A. I have reviewed the correspondence.

Q. So you have seen how FDA -- how Boehringer has submitted modeling information to the FDA?

A. I have seen over time that that has been submitted.

Q. So come back to my question. My

HARVEY

question is can you point me to any specific regulatory action that FDA has taken regarding Pradaxa in response to receiving that modeling information?

MR. MOSKOW: Objection to form.

A. Now, is this independent of the PK information that led to the approval of the 75-milligram, or are you including that? Because of course there wasn't a 75-milligram dose study that was done based upon PK modeling.

Q. You raise a very good point, Doctor. So let me take a step back. You understand that every piece of plasma concentration data from the RE-LY study was submitted to the FDA pre approval; correct?

A. That's my understanding.

Q. And it was that data that the FDA carefully analyzed, and not only did they discuss that data in the context of approving the 150-milligram dose, they actually approved a whole new dose based on that data, the 75-milligram dose; correct?

A. That's what -- yes.

HARVEY

Q. What you are objecting to is not the withhold -- and the later modeling was all based on that same data, right, from the RE-LY study?

A. That, I don't know because I don't know whether it was the original data set, the resubmitted after the refuse to file, and -- or some of these subsequent analysis. I would hope it's all based upon the same data which, of course, is with the first generation product, which is not what's currently now being marketed.

Q. Well, that's false, isn't it?

A. It was -- the original data set was based upon the first generation product.

Q. I didn't ask you about first generation, Doctor. I just asked you about the plasma concentration data.

Do you know of any plasma concentration data that has been generated since the time of the RE-LY study?

A. There have been publications. You mean generated by the sponsor or --

Q. By anyone.

HARVEY

A. There are publications that have come out where they have looked at levels, at drug levels as part of their practice, and there are publications.

Q. Are there any -- has Boehringer obtained any data on plasma concentration outside of the RE-LY study?

A. It's my understanding that some of the authors on these papers are BI employees.

Q. But those are -- do you understand those papers that you're referring to to be analysis of the RE-LY plasma concentration data?

A. There was a paper that I reference where they're using -- they're measuring levels as part of their ongoing work.

Q. Which paper is that?

A. I would have to look through.

Q. Was all the RE-LY plasma concentration data submitted to the FDA before approval?

A. I know it was all submitted.

Q. And you understand that the 2014 exposure paper by Dr. Reilly and others was

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based on that RE-LY plasma concentration data?

A. Yes, yes, I do.

Q. Do you understand --

A. I was thinking of a paper from 2016 or 2017.

Q. You understand that the models you've been discussing were based on the RE-LY plasma concentration data?

A. Yes, I do. There was an article from the group in Canada that was measuring levels and monitoring.

Q. Did you have any interactions with BI while you were at the FDA?

MR. MOSKOW: You can answer. There's a question pending.

A. Okay.

MS. PRESBY: You don't have to wait for him.

A. Not that I remember.

Q. Let me just make sure I rounded out my prior questions. We talked about the modeling information ultimately being submitted to the FDA. And I'm focused on the modeling information that was conducted -- strike that.

HARVEY

When you have said that there was modeling information that should have been submitted sooner to the FDA, you're talking about modeling that was done post approval at Boehringer; right?

A. I'm talking about any modeling that might have been done either before, during, or after submission that had significant -- that could have had a significant impact on benefit/risk.

Q. When was it done, Doctor?

A. That's a good question. I mean, I can only go based upon the --

Q. What's your understanding of when it was done?

A. My understanding is that there was some modeling done prior to approval and then there has been subsequent modeling done after approval.

Q. And when that modeling data has ultimately been submitted to the FDA, can you point me to any specific action that the FDA has taken based on that modeling data?

A. No, I can't.

HARVEY

MR. MOSKOW: Objection to form.

Q. You know that the FDA has conducted their own modeling; right?

A. Yes, I do.

Q. For example, that was the basis for the 75-milligram approval; right?

A. Yes, I am aware.

Q. The FDA actually did modeling in the opposite direction as well; right? They looked at maybe it would be good to have an even higher dosage of Pradaxa?

A. Yes, that's -- I've read that.

Q. Do you know if as we sit here right now as a factual matter -- strike that.

All that modeling that we were just discussing was done before Pradaxa was ever approved; right?

MR. MOSKOW: Objection, form.

A. I don't know that.

Q. You don't know that the 75-milligram modeling was approved and done before?

A. I do, do know, but -- then can you clarify, when you were saying all that modeling. Yes, the 75 was done prior to, which

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served as the basis for the 75-milligram approval.

Q. So let me -- you're right. Let me be precise. Prior to approval the FDA did modeling on -- based on Pradaxa blood concentration; correct?

A. That's my understanding.

Q. And that modeling prior to approval led to them approving the 75-milligram dose; right?

A. That's what I understand, yes.

Q. And they also modeled before approval what would be the effect of having an even higher dose; right?

A. There is discussion of that in the memos, yes.

Q. And I take it your point is you don't know if they have done modeling since. They might, they might not have?

A. That's right, I don't know.

Q. So maybe that answers my next question, which is do you even know that the modeling Boehringer has conducted is not entirely redundant to the modeling that the FDA

HARVEY

has independently conducted?

MR. MOSKOW: Objection to form.

A. There's no way for me to know that, being outside the agency.

Q. To ask it differently -- and I always am to be mindful of the objection. Can you point me to any distinct modeling that Boehringer has done that you can tell me that the FDA never looked at this very model or this very issue?

A. There was some modeling discussed internally, and I remember some internal emails from BI where, when the results of the modeling was discussed, the response in the email was that's not consistent with our no-monitoring policy.

Q. I'm going to ask you about that.

A. So my question would be then what was the gap in the amount of time between that email and when that modeling was ultimately submitted.

Q. Boehringer doesn't get reports from the FDA on internal modeling the FDA's conducting; correct?

HARVEY

A. There's no mechanism for that.

Q. So Boehringer doesn't know what modeling the FDA is doing, do they?

A. Unless there is a meeting or a communication.

Q. So my question to you is, can you tell me that Boehringer did any modeling on Pradaxa that was not also independently being done by the FDA?

MR. MOSKOW: Objection to form.

A. There's no way for me to know that.

Q. As we sit here today, you know there have been a number of publications on the RE-LY study; correct?

A. Yes.

Q. There have been follow-on publications of the RE-LY study; correct?

A. Yes.

Q. Boehringer has had various other publications that it's either sponsored or participated in regarding Pradaxa; right?

A. Yes.

Q. There have been a volume of independent scientists publishing on Pradaxa?

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A. That's correct.

Q. Can you point me to any study data that Boehringer has at the company that has not been disclosed through a publication or through clinicaltrials.gov or something like that?

A. Based upon my review of the documents -- which is not every single document because there were millions of documents -- I can't point out anything specifically that wasn't ultimately shared with FDA.

Q. Or with the public, the medical community. That's my question. Is there anything in terms of study data that you saw that's relevant to your opinions that has not been publicly disclosed in some form by a clinical trial, publication or clinicaltrials.gov or something of that nature?

A. I'm not sure --

Q. In terms of studies.

A. Yeah. Clinicaltrials.gov, which I spend a lot of time on, often doesn't actually have the data; they just have the protocol posted. But I'm not sure if some of the modeling for the pediatric studies, whether all

HARVEY

of that has been published. I'm not aware of that.

Q. That's why I asked the question the way I did. Are you aware of any actual study data, safety data that has been generated but not publicly disclosed?

MR. MOSKOW: Objection to form, asked and answered.

A. I guess I'm having trouble with your distinguishing between modeling and data. And it's interesting because in the current debate over FDA process and industry trying to increase the ability to use real-world data and others, PhRMA, which is an organization which I believe BI is a member of, has been advocating that modeling data is data. So I don't make that distinction between data and modeling because modeling is another form of data as part of this big data initiative in order to help facilitate using that type of information for approvals and post market.

Q. I will draw that distinction. Is there any underlying data you can point me to that you looked at that's relevant to your

HARVEY

opinions that's not been publicly disclosed?
A. I'm not aware that all of the information in the pediatric development program, including that modeling, has been disclosed.
Q. Anything else?
A. No.
Q. And the pediatric program is an ongoing study; right?
A. That's correct.
Q. And it's not customary to disclose study results in all instances before they're final; correct?
A. That's not routine, but of course in this case, it has impact -- some of what's being learned in the pediatric space about dose and corresponding drug levels could actually then impact what's known or what should -- you know, could be done in adults. So they're not distinct that one -- you know, that some something that happens in one area could inform another.
Q. You've -- just to be clear, what you're referring to as modeling in the

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pediatric study is a dosing algorithm; correct?
A. That's part of what I'm --
Q. Okay. What modeling from the pediatric study are you referencing beyond a dosing algorithm?
A. As I looked at the pediatric plans, there was a lot of discussion regarding how that was going to be done, and that was in light of some of the earlier adult modeling being called preliminary. And then it was used -- turned around and that same sort of modeling was then used to help determine a therapeutic range and dosing for the pediatric patients.
Q. Is it your understanding that the pediatric dosing is based on a model as opposed to just cut points in terms of plasma concentration from the RE-LY study? Is that your understanding?
A. Well, I think once again, you know, you using the term "model" is imprecise. There was --
Q. It's your term.
A. I mean, it -- the -- there wasn't

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actual dosing in kids to determine the lowest and highest dose. It was done through a mechanism where there was modeling and PK data.
Q. Wasn't it just done by saying let's make sure that pediatric patients fall, in terms of their blood concentration, within the 10 to 90th percentile of RE-LY?
MR. MOSKOW: Objection to form.
A. I don't know if that's an accurate characterization. Sounds like an oversimplification.
Q. Do you know that it is?
A. I don't -- that doesn't seem to be consistent with what I was reading.
Q. Why don't you articulate on the record under oath for me how you understand the dose was selected for pediatric patients.
A. The question I was answering that you asked was am I aware of data that has not been released. And I think we've already established that I'm not an expert in modeling.
Q. Can you now answer my question?
Do you know how the dose was selected in the pediatric trial?

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A. I don't know the specifics of how it was done but I know it was based upon -- it was not based upon traditional dose ranging in children.
Q. Can you tell me anything about how it was done?
A. It was based upon some of the modeling data which we have been discussing, and a range, and what would be a safe range for children. I don't have additional details beyond that.
Q. What was the range?
A. There was a discussion of 50 to 225, which was of course different from Dr. Temple's sweet spot of 50 to 150 or 75 to 150.
Q. Do you know how they got to 50 to 225?
A. That was part of the PK and the modeling process. That was my understanding.
Q. Do you know if there was any model that led to 50 and 225 as opposed to just picking points on the curve of where patients in RE-LY fell on plasma concentration?
A. Not being an expert in that area

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which, we've already established, I don't know the specific details.

Q. And what's that area where you're not an expert?

A. In actually conducting modeling.

Q. Okay. You've been an expert witness against Boehringer in the past; correct?

A. I have been involved with a patent dispute, and it was in U.S. Patent Court. And I was retained by the innovator to discuss the FDA approval process for that innovator product. And there were a number of companies who were biosimilars makers that were on the other side of that patent dispute, and BI was one of those companies.

Q. So is the answer to my question yes, you have been an expert against BI in the past in a patent case?

A. In a patent case.

Q. And how much were you paid in that patent case?

A. I was paid -- well, the two cases were together, and so the work that I did for one had direct bearing on the other. If I

HARVEY

remember correctly, there were -- it was about 100 or so hours, so that would have been about 50, 60,000.

Q. And do you know what the outcome of that case was?

A. The U.S. Patent Court actually decided against AbbVie.

Q. Against the side you were --

A. The side I was referencing.

Q. Have you ever been a party to a lawsuit?

A. As far as -- can you --

Q. Plaintiff or defendant?

A. I have been involved with one malpractice case when I was at Anne Arundel. I was one of many physicians who treated a patient. And I was dropped. After depositions and expert testimony or expert depositions, I was dropped from the case because I was found that I met or actually exceeded the standard of care.

Q. I will represent to you that -- well, I'm not going to quibble with you about that. What was the nature of the injury in that case?

HARVEY

A. It was a patient who came to the hospital with a dissection of the aortic aneurysm.

Q. Did you give testimony in that case?

A. No, I did not because I was dropped before that.

Q. You've worked full-time as an independent regulatory consultant from 2015 to the present?

A. That's correct.

Q. Can you tell me the pharmaceutical companies other than Pfizer that you do work for?

MR. MOSKOW: I just want to note for the record to the extent you're not subject to a confidentiality agreement you can answer that question.

A. Well, I'm working with a -- I mean, all of them I have confidentiality agreements, but I work with large pharmaceutical companies, biotech companies. Most of my work is with companies. I don't have a contract with BI and have not done work with BI, but most of what I do in my consulting work is working with

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companies and working on the side of companies.

Q. Do you solicit companies in any way? Do you do outreach to companies?

A. No, I don't because people come to me.

Q. And in your work -- well, not everyone comes to you. You don't represent the industry; right?

A. Well, I only have so many hours in the day and I have all the work I can do.

Q. Boehringer has never come to you.

A. Not that I know of.

MR. MOSKOW: Not yet.

Q. If Boehringer had come to you with a project is there any reason you would have said no, I won't work with you?

A. Not that I know of. They make some good products.

Q. And if Boehringer had come to you with a project and you were doing work for Boehringer, would that keep you from working for the plaintiff lawyers in this case?

MR. MOSKOW: Objection, form.

A. I would have to check to see.

HARVEY

Q. Check with Boehringer?
A. Yeah.
Q. The reason I ask about your clients -- I understand the concern about confidentiality agreements. So you know, my position will be that if we can't get information on who you represent, you shouldn't be allowed to talk about it in terms of a statement like you just made: I represent a lot of big pharmaceutical companies. So I say that simply to set up my question so you understand where I'm coming from with my question. When you say you represent a number of large pharmaceutical companies, can you tell me who those companies are?
MR. MOSKOW: Objection to form. You can answer if you are able.
A. Okay. I do work for J&J.
Q. What J&J products?
MR. MOSKOW: Again, to the extent that you're bound by confidentiality, you should answer as you see fit.
A. I think that is under confidentiality.

HARVEY

Q. So you'll decline to answer that?
A. Because if they're premarket, I don't know if that's been disclosed or not.
Q. Have you worked on any post market J&J products?
A. No.
Q. Who else?
A. And I can say I'm not working on any anticoagulants. I mean, most of my work is in the GI space, so GI and liver, so -- and Pfizer has been a client.
Q. Who else? We've talked about Pfizer.
A. Right. I've done work for Amgen.
Q. You understand that J&J is a manufacturer of Xarelto?
A. I didn't really think about that.
Q. But do you know that?
A. I do know that now.
Q. Who else?
A. Like I said, my work with J&J has been in the liver space, NASH, NASH disease, fatty liver. Amgen.
Q. What proportion of your work is expert testimony work?

HARVEY

A. It's less than 20 percent.
Q. And is it different in terms of proportion of your income?
A. It's less than 20 percent of my time and it's less than 20 percent of my income.
Q. Do you charge differently for consulting work versus expert testifying work?
A. I have a range for consulting work that can be anywhere from 400 to 600 an hour, and my standard legal rate is 500 an hour.
Q. Have you ever done any other case like this where someone is alleging injury from a medicine?
A. Not from a medicine, no.
Q. From a device?
A. From a device.
Q. What was the device?
A. The device was the Olympus endoscope where there were -- I was asked to advise on whether or not they should have submitted a new 510(k). And it was my opinion that the change warranted a submission of a 510(k).
Q. Any other cases where someone's alleging injury from a product?

HARVEY

A. Not that involved any company.
Q. So --
A. So there was a case -- and these are all listed in my report. There was a case in Connecticut where I worked for the plaintiff, for the family, you know, the Radzik case, and it had to do with Remicade. And it had to do with the FDA label for Remicade and the approval of the pediatric indication, which I did as the GI division director, as well as the placement of the black box for hepatic splenic T-cell lymphoma. And that was -- and Remicade is a J&J product but they were not party to the suit, which is why I was able to do that.
Q. If they were party would you not have been able to do that because of your work for them?
A. I would have had to check with them.
MR. SCHMIDT: I marked as Harvey Exhibit 3 your prior testimony which I think you were just referencing.
(Harvey Exhibit No. 3 was marked for identification.)
BY MR. SCHMIDT:

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Q. Is that, in fact, what Exhibit 3 is?
A. Yes, it is.
Q. Any other testimony -- strike that.
Am I correct that all your testimony in cases involving injury from a product has been on behalf of a plaintiff against a company?
A. So the two examples are plaintiff against a company.
Q. Have you done any consulting for Bristol-Myers Squibb?
A. I have not, but, you know, I -- I have -- there are emails of them reaching out to me to do some work, but I haven't -- I haven't talked with them yet or entered into any agreement yet.
Q. Would that relate to Eliquis?
A. It -- it's in -- with NASH, so fatty liver disease.
Q. So not Eliquis?
A. Not Eliquis.
Q. Okay. Have you ever done any work for Bayer?
A. I have interacted with Bayer back

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when I was at FDA because they were one of the makers of Naproxen, but I have not consulted with Bayer since leaving Pfizer. So as an independent consultant I'm not currently working with Bayer.
Q. And you're affiliated with a group called NDA Partners?
A. There are several groups. One is NDA Partners, which contain a number of ex-FDA people, including Carl Peck. I work with Kinexum, which is -- many of which are ex-FDA. I work with Uroncor (phonetic), which are many ex-FDA people. Then I work with a group called xFDA, which are ex-FDA people, and then do things on my own as well.
Q. So that's four different groups that you have an affiliation with?
A. Yes.
Q. And do you understand that all four of those groups hold out their members as offering professional expert testimony?
A. I'm familiar that that's the case with NDA Partners. I haven't had that experience yet at Uroncor or Kinexum.

HARVEY

Q. What is their purpose?
A. Mostly to help, you know, small companies navigate the FDA regulatory process.
Q. Let's talk about your work in this case. I'm going to mark your deposition notice. Did you ever review your deposition notice in this case?
A. Yes, I did.
Q. Did you look at -- the part I care about -- it will be Exhibit 4 -- is the document request that accompanies it?
A. Yes.
Q. Did you purport to provide your lawyers with all the responsive documents to that document request?
A. Yes.
(Harvey Exhibit No. 4 was marked for identification.)
BY MR. SCHMIDT:
Q. And those have been produced pursuant to our protocol?
A. That's my understanding.
MR. SCHMIDT: I take it you'll make that representation?

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MR. MOSKOW: Correct. I just want to make clear to the extent that a prior question suggested that a company that he is with -- affiliated with, like NDA Partners, if they provide some sort of advertising material, we didn't think that was responsive to the specific request.
MR. SCHMIDT: Okay.
Q. When were you contacted by the plaintiff lawyers in this case?
A. It was back in 2016.
Q. Do you remember when in 2016?
A. It would have been sometime in the fall, you know, summer, fall. And I didn't do my first review work -- I looked back at the invoices so I could answer this sort of question. I think the first time I billed for review was November 16, 2016.
Q. And have you worked reasonably continuously on this matter since November 2016?
MS. PRESBY: Object to form.
A. There are some months that have been

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busier, and obviously writing the report, and then there was a little bit of a lull and then of course now gearing up for the deposition. So -- but it's been pretty much something every month for the last year or so.

Q. Who contacted you?

A. Actually, I think you contacted me. By email. By email.

Q. Do you mind just saying on the record who you're referencing?

MS. PRESBY: It sounds like Paul.

MR. SCHMIDT: It does sound like me. It was not me.

A. Neal contacted me.

Q. Mr. Moskow?

A. Yes, through I think -- I think the introduction was made by Alexander, or Zan, Zan Miller from Kinexum. But he did it as a introduction as opposed to official Kinexum work.

Q. Who is Mr. Miller or Dr. Miller?

A. He's a former FDA person who I'd worked with. He was in the metabolic endocrine division back when I was at FDA.

HARVEY

MR. MOSKOW: Just so we don't go off on a tangent, it's Zan Fleming, Alexander Fleming.

A. Oh, I'm sorry.

Q. Thank you. And is it Dr. or Mr.?

A. Doctor.

Q. Dr. Fleming put Mr. Moskow in touch with you?

A. Yes, by email.

Q. Okay. And did you then have a discussion with Mr. Moskow?

A. Yes.

Q. Over the telephone or in person?

A. First over the telephone and then in person.

Q. Did you agree over the telephone to serve as an expert witness?

A. I don't know if I agreed until we actually had the face-to-face meeting, actually.

Q. At some point you did have a face-to-face meeting?

A. Yes.

Q. And was that done here in Washington?

HARVEY

A. In Chevy Chase.

Q. Pretty tony neighborhood?

MS. PRESBY: Objection to form.

MR. SCHMIDT: Ms. Presby doesn't have the same "outsider looking in on the D.C. neighborhoods" that some of us do.

MS. PRESBY: I'll object to that too.

Q. So was this meeting in Chevy Chase with Mr. Moskow in November 2016 when you started the work or just before that?

A. It was just before that.

Q. Did you agree at that time to become an expert in this case?

A. Yes.

Q. At that point you knew their allegations against the company generally?

A. Yes.

Q. But you didn't know the specifics in terms of reviewing the documents?

A. That's correct.

Q. And at that point, you began reviewing documents, and I guess ultimately

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writing what became your 120-page report.

A. That's correct.

MR. SCHMIDT: We were provided with a billing statement that I've marked as Exhibit 5.

(Harvey Exhibit No. 5 was marked for identification.)

BY MR. SCHMIDT:

Q. Does this show all the work you've performed on Pradaxa as an expert witness for plaintiffs?

A. The only thing to add would be what's happened in the last week or so, but it certainly is current as of -- until --

Q. October 28?

A. I would -- yeah, October 29.

Q. That reflects that you performed 202 hours, 202.5 hours on Pradaxa?

A. Yes.

Q. And you billed over $100,000 for that work?

A. Right, since my standard legal rate is 500 an hour.

Q. So in the year or so that you've been

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working on Pradaxa, you've made $100,000 from that work?

A. That's correct.

Q. And that includes your document review and that includes writing your report and that includes meeting with these fine lawyers?

A. That's correct.

Q. I would imagine it takes a good bit of time to write a 120-page report.

MR. MOSKOW: Objection to form.

A. It took over 90 hours, yeah.

Q. And that's where I was going. Are you able to -- I think you just did. Are you able to articulate how much of the 202 hours you spent was actually spent writing the report versus reviewing documents and conducting research?

A. Right. Well, so I went back to my invoices and it -- about 92 hours were for writing the report, but part of writing the report is also then referring to the documents. But the time when the report -- when I created the report, that was 92 hours. And then there

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were many documents to review and then there were other documents which then became available to be reviewed, and so that's how we got to the 202.

Q. As I understand it, you had some help compiling some of the documents and focusing on certain parts of the documents from the lawyers; is that correct?

A. I received, you know, technical help and nuts and bolts, cutting and pasting, and if we had a discussion and I pointed out certain areas that I wanted to focus on, you know, certain excerpts from expert depositions and certain emails, they were the ones that did the cutting and pasting into the document.

(Harvey Exhibit No. 6 was marked for identification.)

BY MR. SCHMIDT:

Q. I'm passing you what I've marked as Exhibit 6, which is a series of schedules that were attached to your report. And I believe you said in your report these were prepared under your supervision by lawyers; is that right?

HARVEY

A. Yes, that's correct. I didn't do any of my own photocopying.

Q. Let's take a look at one of these. Schedule 4 is a summary of label changes. Do you see that?

A. Yes.

Q. This was prepared by the lawyers for you?

A. Yes, it was.

Q. Did you go through looking at the individual labels to quality check this to make sure it was accurate in all regards?

A. Well, I had -- when I do my review of labels, I usually do it online on the FDA website. And when I went through and looked at this summary, this was consistent with my review of the labels.

So did I hold the chart up to the FDA website and do a word-for-word comparison? No, but there was nothing I read in this that was not consistent with my review of the FDA labels on the -- or the labels on the FDA website.

Q. Okay. Look with me, if you would, at Schedule 7 and Schedule 11, if you just want to

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pull those out and put them in front of you.

A. 7 seems to be missing. I have 5, 6, and -- oh, there's 7. There we go.

Q. So look at 7 and 11, please. Do you mind grabbing 11 as well? It's at the bottom of the stack. 7 and 11 are summaries of documents and emails. Number 7 relates to second generation Pradaxa. Number 11 relates to modeling, specifically modeling by someone named Thorsten Lehr.

Do you see that?

A. Yes.

Q. And these summarize documents on those two issues; correct?

A. Yes.

Q. Or contain excerpts from documents on those two issues; correct?

A. Yes.

Q. Who prepared these?

A. So we had some face-to-face meetings. We talked about the various emails. I highlighted certain emails that I felt were important from a regulatory perspective. And based upon that direction, this document was

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created. And so they -- the counsel's office did the cutting and pasting.

Q. Did you review the full documents that are reflected in these exhibits, these schedules?

A. I read through the information and, you know, there was extensive number of documents, and there may have been times I was skimming for certain information, and other times I read more intently.

Q. Do you know that the documents you reviewed to prepare Schedule 11 and Schedule 7 were the entire set of relevant documents on those issues, Thorsten Lehr's modeling and second generation?

A. Those were the documents I was provided to review.

Q. For example, Schedule 7 does not reference -- regarding second generation does not reference any FDA documents, does it?

A. That's my understanding.

Q. Have you read FDA documents on second generation?

A. I have read the documents that were

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provided, which included some of the discussion about the FDA reviewer's review of the data and how it fell outside the 80 to 125 range.

Q. Let's be precise, Doctor. You quote, I think, an email someone wrote getting into a cab after a meeting with an FDA person and some other BI documents talking about the FDA; right --

MR. MOSKOW: Objection to form.

Q. -- in Schedule 11?

A. I don't know about the cab. I know there were documentations of a discussion and, you know, there was a very thorough documentation in 2011 where a BI individual wrote down what the cardiovascular division wanted to see as a path forward, but I don't know where that was written or any of those details. But there were correspondence from FDA, or there were correspondence -- I guess actually a more accurate reflection, there was information from FDA that was in internal documents, their understanding of what FDA said.

Q. Path forward has nothing to do with

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second generation, does it?

A. Path forward?

Q. You just talked about a path forward. That discussion that you're referencing has nothing to do with second generation, does it?

A. That had to do with the 110 dose.

Q. Right. Nothing to do with second generation, does it?

A. Well, it does, because I would assume they're not going to have the first generation of the 110 while they're now marketing the second generation of the 150.

Q. Do you know that?

MR. MOSKOW: Objection to form.

A. My understanding is that they went from the first generation to the second generation because the second generation was what they wanted to market.

Q. Were there ever second generation discussions with the FDA about the 110 dose, sir?

MS. PRESBY: Objection, form.

A. No, because the 110 dose was not approved.

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Q. So focus on the second generation document that you have in front of you. Does that reference any actual FDA documents --

MR. MOSKOW: Objection to form.

Q. -- reflecting their review of the second generation and whether it was bioequivalent to the first generation?

A. The focus of this document is the company's correspondence and discussions.

Q. So is the answer to my question no, Schedule 11 does not reference any FDA documents regarding second generation or bioequivalence?

A. Yes, that's correct.

Q. Have you reviewed any FDA documents regarding bioequivalence in second generation?

A. Yes, I have.

Q. For example, have you reviewed the FDA's clinical pharmacology review memo that discusses that issue?

A. Yes, I have.

Q. And what was the FDA's conclusion about whether the second generation was bioequivalent to the first generation?

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A. Well, I would be happy -- if you gave me that document, I'd be happy to point it out, but my memory is that the reviewer found that it did not meet the 80 to 125 -- 125 range. It came in actually around 126, which is outside the range. And under standard procedure, that should have led to a request for clinical bridging, clinical data. And by reading the memo, I'm not quite sure why then the leap was made that it was going to be close enough.

Q. Have you ever performed bioequivalence review for the FDA?

A. I have reviewed -- as a division director, I have to review the work of others.

Q. Have you ever performed yourself bioequivalence review where you're the one responsible for undertaking the review, not reading someone else's work?

A. I have not.

Q. Okay. Did you see that the FDA reviewer who had that as a job and had that expertise made the conclusion that the first and second generation products are bioequivalent?

HARVEY

A. Yes, I do.

Q. Do you know what that means, that they're bioequivalent?

MR. MOSKOW: Objection to form.

A. Well, the fact that it fell outside the range of 80 to 125 means they're not, but the reviewer felt they were.

Q. Move to strike as nonresponsive. Do you know what it means for drugs to be bioequivalent?

MR. MOSKOW: Objection to form.

Q. For products to be bioequivalent?

MR. MOSKOW: Are you asking regulatory context or in scientific context?

Q. Do you know?

A. In the regulatory context --

Q. Sure.

A. -- or the scientific context?

Q. In the FDA context.

A. In the regulatory context --

Q. Let me take the question back and ask it differently. You said there were occasions where -- do you have the expertise to conduct a

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bioequivalence review?

A. Actually, based upon my experience at FDA, my Ph.D. in biochemistry and my medical training, yes, I do.

Q. But you never did it?

A. I never did it.

Q. Okay. When work would come to you from FDA reviewers who that was their job, to determine if products were bioequivalent, and they would say to you, in their work, I have determined that this product is bioequivalent, what did you understand that to mean?

A. That based upon the data provided to them, they felt that it was in a range of sameness.

Q. Okay. And that was the conclusion that the FDA reached regarding the second generation, that it was bioequivalent or in a range of sameness to the first generation; correct?

A. That was their finding.

Q. And have you seen any -- you know there's been a substantial volume of real-world data on Pradaxa?

HARVEY

A. Yes.

Q. And that real-world data by definition involves the second generation formulation; right?

A. That's correct.

Q. Have you seen any real-world data that suggests that there is a meaningfully different safety profile of the second generation product than there is from the RE-LY study which was first generation?

A. But there's no way to know that because the first generation product was studied in clinical trials where you have a numerator and denominator. The second generation product is being reported under adverse event reporting, MedWatch and others, where there's no denominator data. So you know the absolute number of events, so there may -- but you don't know the rate.

Q. Sir, have you -- are you telling me that you have reviewed the epidemiological real-world data on Pradaxa, published by some of your former colleagues at the FDA as well as by other independent scientists?

HARVEY

A. What's the question? Have I read it or do I know it exists?

Q. Have you read it?

A. I've read some of the publications through FDA.

Q. And you know there's a number of those publications; right?

A. Yes, I do.

Q. And those publications do include a denominator. They compare people who have taken Pradaxa to people who haven't taken Pradaxa in a real-world epidemiological setting; correct?

A. Yes, I do.

Q. And have those shown that the rates of bleeding in Pradaxa are any different in a meaningful way than what was seen in the RE-LY trial?

A. Let me ask for a clarification. Since their denominator is a made-up denominator, and there's a lot of debate within FDA whether it's a -- whether it's valid to take, you know, data, IMS data, prescriptions, use that as a denominator, because that's not a

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true ratio. It's something that's often debated within FDA. They published it. It's a working hypothesis. But it's not a valid comparison between a rate obtained in the post market setting and the rate obtained in a clinical trial. And this has come up over and over again.

Q. Move to strike as nonresponsive. Sir, have you seen --

A. So my experience --

Q. Let me ask my question, please. Have you seen any epidemiological real-world data comparing Pradaxa patients using second generation to patients using something else like warfarin, that suggests that the second generation has higher bleeding rates than the first generation?

MR. MOSKOW: Objection to form.

A. I know of no valid comparison of the first generation and second generation because it was not studied in a clinical trial.

Q. Move to strike as nonresponsive. Try to answer my question now, sir.

A. I'm trying.

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Q. I'm just asking you about -- you have seen bleed rate data --

A. Yes.

Q. -- from real-world epidemiological studies; correct?

A. Well -- and you can understand my confusion.

Q. No, I can't.

A. Moments ago, real-world data and modeling data wasn't data, and now it's data.

Q. Sir, I'm going to ask you not to argue with me, especially on nonsensical grounds. I'm trying to ask you simple, simple questions. I didn't ask you anything about modeling just now. I don't mean to say nonsensical but I didn't ask anything about modeling.

So here's -- I'm going to try to ask really simple questions and I'm going to ask you not to argue with me. Just see if you can answer my question.

My first question is, you understand that there have been real-world epidemiological studies that compare bleed rates in patients

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taking Pradaxa to bleed rates in patients taking warfarin; correct?

MR. MOSKOW: Objection to form. You can answer.

A. Yes, I understand that.

Q. And you understand that when they look at Pradaxa patients, those are Pradaxa patients who have used the second generation product; right?

A. That is correct.

Q. And you understand that those studies have generated rates of bleeding in those second generation Pradaxa patients versus bleeding rates in warfarin patients; right?

A. Yes.

Q. Are those bleeding rates, are they occurring differently than what was seen in RE-LY, that compared first generation Pradaxa with warfarin?

A. In the average patient, which is what they're looking at, there is no difference in -- there are similar rates in the average patients.

Q. In fact have you seen repeated

HARVEY

conclusions in those epidemiological studies that these are consistent with what we saw in RE-LY?

MR. MOSKOW: Objection to form.

A. I have seen those conclusions.

Q. Including by your colleagues or your former colleagues at the FDA; right? Like Dr. Graham who we talked about?

A. Yes, that's correct.

Q. Thank you.

Do you disagree with the FDA's conclusion that Pradaxa second generation was bioequivalent to Pradaxa first generation?

A. Yes, I do.

Q. Schedule 9. Do you have Schedule 9 in front of you? Funny thing, it says 12, and I'm told that the proper reference is Schedule 9.

MR. MOSKOW: That's correct.

Q. Do you have it there?

A. Yes, I do.

Q. This is a summary of deposition testimony; is that right?

A. Yes.

HARVEY

Q. And tell me what this reflects.

A. This is when I went through the various depositions, these are the areas that I called out as having some meaning to me from a regulatory perspective.

Q. Got it. Did you review all the depositions?

A. I read through them, and there are times when I might have skimmed through because some parts of the depositions were more informative than others.

Q. Let's look at an example. If you look at page -- I should have written this down. It's toward the back. I'm looking for Paul Reilly. Help me find Paul Reilly.

MR. MOSKOW: I think he was deposed both first and second, so he's going to appear twice.

MR. SCHMIDT: I think he's just in here once.

MR. MOSKOW: That would be on page 62.

MR. SCHMIDT: Yeah.

Q. Look with me at page 62. Thank you.

HARVEY

Do you see there's two questions and answers from Dr. Reilly?

A. Yes.

Q. Mr. Moskow just made note of the fact that he was deposed years apart on two separate occasions. Did you know that?

A. I remember that coming up in conversation at some point.

Q. I think I'm right -- Mr. Moskow will tell me if I'm wrong -- both depositions were multi-day depositions.

MR. MOSKOW: I believe the second was a single day.

Q. He was deposed across multiple days across multiple years. Did you know that?

A. I wasn't aware of those details, or if I was it didn't -- it didn't strike me as significant.

Q. Here's my question. Do you know that you read all his testimony?

A. I don't think I read every word but I went through it.

Q. Do you know that you had access to all his testimony?

HARVEY

A. I had access to everything.

Q. Just as an example, you've quoted here questions and answers from three pages. Do you have a volume, a sense of the volume of Dr. Reilly's testimony?

A. It was extensive.

Q. It was 1,500 pages. You can't say you read the full 1,500 pages, can you?

A. I think I just told you that.

Q. That you did not?

A. That I did not. There were areas I skimmed if I didn't think it was informative.

Q. And that's true for other -- for -- generally for the depositions; right?

A. That's correct.

Q. Now, the parts that you picked out, let me just ask you a question about these two excerpts you have. The first question relates to the timing of the reversal agent; correct?

A. That's correct.

Q. Did you read his full testimony on the timing of the reversal agent or just this question and answer?

A. As I said, I sort of looked through

HARVEY

and I read and I skimmed and then stopped and focused and then continued.

Q. But come back to my question. My question is do you know that you read his full testimony on the timing of the development of the reversal agent, as opposed to the single question and answer that you've snipped out here?

A. I've read his testimony, and this quote is consistent with what I read.

Q. Well, do you know if he talked about different antibodies, for example, that were explored in terms of developing a reversal agent, or just the one you reference in this single question and answer?

A. There was a lot of general discussion. I didn't focus on that and didn't have it as the basis of my report. It was the fact that that took place a number of years before the NDA was submitted to FDA. So it was the timing that was for me important, not whether it was the first or second cell line that was used or the way antibodies were made.

Q. You picked out this single question

HARVEY

and answer from Dr. Reilly on the reversal agent development. You didn't study his full testimony in great detail on the reversal agent development; fair?

A. That's correct.

Q. Let's look at the second question and answer. And that's something you actually quote in your report. You can put this aside. And I'm not going to ask you any more about these schedules because they're kind of bulky. But go back to your report at page 103, footnote 97. You will see there that you quote the same question and answer from Dr. Reilly that was the second question and answer in your Schedule 12/9 in Exhibit 6.

A. I'm sorry. Can you repeat the page number?

Q. Of course. Page 103, footnote 97.

(Discussion held off the record.)

BY MR. SCHMIDT:

Q. Are you with me on page 103?

A. Yes, I am.

Q. Do you see that quote from Dr. Reilly, the second quote in your Exhibit --

HARVEY

Schedule 12/9 from your Exhibit 7?

A. Yes.

Q. The quote is: "When you're doing this work do you weigh bleeds differently than you weigh strokes?

"I do not."

Do you see that?

A. Yes, I do.

Q. And in the text that accompanies that quote, you actually state the proposition more broadly. You say that Dr. Reilly generally weighs, quote, strokes and life-threatening bleeds equally.

Do you see that?

A. Yes.

Q. Do you know if that's a true statement?

A. It was my understanding based upon what I had read in his deposition and based upon the articles of which he is co-author.

Q. So let me see if I have that. When you say he weighs bleeds and strokes equally as a general matter, what do you mean by that?

A. That as he was quoted: "When you do

HARVEY

this work do you weigh bleeds differently than you weigh strokes?" And he goes "I do not."

Q. What is "this work"?

A. The work he does at BI.

Q. So --

A. With anticoagulant.

Q. So is it your understanding when he assesses risk and benefit for Pradaxa, as a general matter he weighs strokes and bleeds equally? Is that your understanding?

A. That's my understanding from his testimony, his sworn testimony.

Q. Okay. And referencing that sworn testimony, you see that I focused on the first part of the question, which is "when you're doing this work."

Do you see that?

A. Yes.

Q. You understand "this work" to refer to his general Pradaxa work as opposed to one specific analysis? Or do you know?

A. I felt it was all related to Pradaxa.

Q. His general Pradaxa work as opposed to a specific analysis he conducted?

HARVEY

A. I didn't make that distinction.

Q. Okay. You agree that it's the FDA's mission to protect consumers in the U.S. from dangerous drugs?

MR. MOSKOW: Objection to form.

A. The mission statement since 1998 is to both promote and protect.

Q. Do you agree with me, though, that their mission -- they have a mission of protecting consumers from dangerous drugs?

MR. MOSKOW: Objection to form, asked and answered.

A. It's -- "dangerous drug" doesn't appear in their mission statement. But it's their job to promote and protect the public health and to make sure that drugs have a favorable benefit/risk, or that the risks -- or the benefits outweigh the risks.

Q. So is it true or false to refer to FDA's mission of protecting consumers from dangerous drugs?

MS. PRESBY: Objection, form.

MR. MOSKOW: Objection, form.

A. Danger -- there's no regulatory

HARVEY

definition that I know of of dangerousness. So they have a mission to protect against drugs where the benefits don't -- or the benefits don't outweigh the risks.

Q. Look with me if you would at page 10 of your report, Exhibit 1. And if you look at the end of paragraph 30, do you see where you write, quote, the very language I have been reading that you have been quibbling with: "FDA's mission of protecting consumers from dangerous drugs"?

Do you see that? It's the very last words in paragraph 30.

A. Paragraph 30? On what page?

Q. 10.

A. Oh. Well, that's --

Q. Do you see that?

A. Yeah.

Q. Is that accurate, that you wrote that the FDA's mission includes protecting consumers from dangerous drugs?

A. I guess I -- I was looking for you for me a definition of -- of what you mean by dangerous. And of course I cite that here, so

HARVEY

now I know the context.

Q. Do you agree with that statement --

A. Yes.

Q. -- that it's the FDA's mission to protect consumers from dangerous drugs?

A. Yes.

Q. Do you agree that the FDA has substantial authority over the approval, labeling and promotion of pharmaceutical products?

MR. MOSKOW: Objection to form.

A. Yes.

Q. Do you agree with me that, in fact, under the law as it has existed for close to a decade now, maybe a decade now, the FDA has a legal obligation to order a label change when they believe one should be made?

MR. MOSKOW: Objection to form.

A. The term "legal obligation" -- they have the authority. In 2007 under the PDUFA legislation at that time that became law, they were granted additional authority where they could unilaterally impose it.

Q. Right. And in fact, they are charged

HARVEY

with, if they become aware of new safety information that they believe should be included in the labeling of the drug, they shall promptly notify the company to make the change; right?

A. Yes.

MR. MOSKOW: Objection to form.

A. That's my understanding.

Q. That's a serious obligation that the FDA takes seriously in your experience; right?

A. Yes, they do.

Q. Their obligation that if they learn of a new safety issue that's not reflected in a company's labeling, to notify the company to change the labeling to reflect that safety issue?

A. Yes.

Q. Are you aware of any instances where the FDA has exercised that authority with respect to Pradaxa and safety information regarding Pradaxa?

A. I'm not aware of that.

Q. Are you aware that, I believe it was 2014, the FDA ordered that there be a black box

HARVEY
warning on Pradaxa?
A. I understand that there was class --
Q. Let me --
A. -- class labeling --
Q. Let me pull back my question because I asked it wrong. I apologize for interrupting. Are you aware that in 2013 the FDA ordered a black box warning for Pradaxa?
A. I understand that as a broader review of the class there were black box warnings placed on the various labels.
Q. And did you understand that black box warning had nothing to do with bleeding risk?
A. I understand that the initial black box had to do with abruptly stopping Pradaxa or the others, and how that increased your risk of stroke -- no thanks -- and then a subsequent addition to the black box was about epidural, subdural injections.
Q. Nothing about bleeding; right?
A. There's nothing currently in the black box about bleeding as of today.
Q. And the warning that the FDA directed in 2013 on -- in the black box was actually a

HARVEY
warning about it's dangerous to stop using an anticoagulant like Pradaxa too quickly --
A. Yes.
Q. -- because you could have a stroke?
A. That's just what I said.
Q. Okay. And that's accurate?
A. Yes.
Q. You're aware, and I'm going to just mark an exhibit. Hopefully we can go through this very, very quickly. You're aware that the FDA has approved Pradaxa or new indications for Pradaxa or the labeling for Pradaxa on different occasions since 2010; correct?
A. Yes.
MR. MOSKOW: Objection to form.
A. That's correct.
Q. I trust you haven't taken the time to count up the number of approvals. Have you?
MS. PRESBY: Objection.
A. As I looked at the FDA website, at drugs, there were well over 10 applications which included labels.
Q. Okay. Just so we have it for the record, I'm going to put those in front of you,

HARVEY
the ones that I have been able to compile. I get to 17 so I'm going to give you the different approval letters and just ask you to count them up.
A. It's well over 10.
Q. You're absolutely right. I just want to get the exact number for the record.
MR. MOSKOW: After we go through this, can we take a break?
MR. SCHMIDT: Sure.
Q. Let me -- we're going to find those on a break. Let me ask you one other question while we're on this subject.
A. Schedule 3 has all the Pradaxa labels.
Q. I want to get you the actual letters so we mark them. You talk in your report about in addition to approving Pradaxa labels, the FDA has also issued various safety communications regarding Pradaxa; correct?
A. Yes.
Q. I think you summarized those safety communications in your report on -- help me out, somebody, anybody. Mr. Hailey.

HARVEY
Dr. Harvey. I believe you summarize them on page 28 of your report.
Do you see that?
MR. MOSKOW: Bottom of 27, top of 28.
A. That's correct.
Q. By my count of your list, the FDA has on at least 11 occasions issued what you described as communications regarding -- different forms of communications regarding Pradaxa to the public.
A. That's correct.
Q. And in every one of those communications, they have reaffirmed that -- their belief that the benefits of Pradaxa outweigh the risks of Pradaxa; correct?
A. That's my understanding.
MR. SCHMIDT: I now have the letters. Let me pass you the letters and then we'll take a break.
(Harvey Exhibit No. 7 was marked for identification.)
BY MR. SCHMIDT:
Q. We've marked the letters as

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Exhibit 7. And let me give you a moment to look through them. But as you look through them I will just say for the record that these are various forms of FDA approval letters starting in October -- starting on October 19, 2010 and continuing up through the present date. This is what we understand to be the set of various forms of approval letters. Is that accurate?

MR. MOSKOW: I'm going to object to form.

A. So 17, I can confirm 17 labels.

Q. Since the approval of Pradaxa, 17 -- strike that.

Including the approval of Pradaxa and in the time since, there have been at least 17 different approval letters at different points in time from the FDA regarding Pradaxa?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. Every one of those approval letters directs Boehringer to use the labeling word for word as approved by the FDA; correct?

MR. MOSKOW: Objection to form.

HARVEY

A. I'm not sure what that means.

Q. Okay. Well, let's look at the first label -- at the first letter in the stack. Do you see on the front page it's got a heading "Content of Labeling"?

A. Yes.

Q. And it says that when the company submits its final label for purposes of the FDA, that label has to be identical to the label that the FDA has approved; correct?

A. Yes.

MR. MOSKOW: Objection to form.

Q. And if you look at the next letter, there's similar language in the next letter; correct?

A. Yes.

Q. And that's standard language for the FDA when it approves new medicines or when it reapproves a label or approves a new indication for a medicine, it directs the company to use the labeling as approved word for word by the FDA; right?

A. Yes.

Q. In fact, every one of these letters

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has some variant of that language directing Boehringer to use the language directly as approved by the FDA word for word; right?

A. Yes, that's the boilerplate language.

Q. But that's -- you say boilerplate. That's a serious obligation on the part of the company. They've got to follow that; right?

A. They -- based upon this action letter, they need to follow that unless new information becomes available and they either submit an sNDA labeling or, you know, if they initiate a label change, but to be compliant with 21 CFR 314.70.

Q. Okay. So let me see if I have that in lay terms. Then we can break. The FDA tells companies like Boehringer you need to use your label as we have approved it word for word. It can be changed later based on new safety information if the company gets advanced approval for the change or, in certain circumstances, the company can do something called changes being effected where it makes a change and then gets later FDA approval; right?

A. That is correct.

HARVEY

Q. But ultimately the FDA has to approve the labeling; right?

A. Yes.

Q. That mechanism that I referenced where the company can unilaterally change a label subject to subsequent FDA approval, the changes being effected mechanism, are you familiar with that?

A. Yes, I am.

Q. Historically has it been widely used by companies?

MS. PRESBY: Objection to form.

Q. Where they implement a CBE -- that's the acronym; right?

A. Yes.

Q. Historically has it been widely used by companies where they implement a CBE label change without first discussing it with the FDA?

MR. MOSKOW: Objection to form.

A. I can't say across every company. Pfizer used it where appropriate. Sanofi used it where appropriate. Discussions at PhRMA, you know, the pharmacological industry

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organization of which BI is a member, discussions there, it was used. And the belief was that the individual company who knows the product best, if there is a safety signal that they wanted to communicate, that's the best way to do it, because then you don't delay transmission of that information.

Q. Has Boehringer ever used a CBE for Pradaxa, a CBE label change?

A. I would have to look back at the records. I would hate to say no, but it didn't jump out at me as significant, but they certainly had the opportunity and they may have used it for something.

Q. You just don't know?

A. I can't remember.

MR. SCHMIDT: Okay. Let's break there.

THE VIDEOGRAPHER: We're off the record at 11:55.

(Recess taken.)

THE VIDEOGRAPHER: Here begins media number 3 in the video recorded deposition of Dr. Brian Harvey. We're

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back on the record at 12:10.

BY MR. SCHMIDT:

Q. Doctor, I'm going to switch gears a little bit. You offer yourself in this case as a regulatory expert; right?

A. That's correct.

Q. And I take it you would take the position that you're here motivated by safety concerns and not just because you're being paid for your testimony?

A. That's correct.

Q. On page 25 of your report, Exhibit 1, you say at the beginning of paragraph 77 that "the current label and each Pradaxa label since product launch does not adequately warn/instruct as to the appropriate dabigatran plasma concentration levels." Did I read that correctly?

A. Yes.

Q. Below that you say: "The language is inadequate for safe use because it does not mention a dabigatran plasma concentration therapeutic range or concentration cutoff values, a low point and a high point."

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Do you see that?

A. That's correct.

Q. What is the range that should be included in the label?

A. Well, I think the first step is to have some sort of cutoffs, high or low, and then that can be refined to a range based upon the data. And part of my thinking was based upon my review of the company's core data sheet. So the stepwise approach that they used to create that document. And based upon my time in industry, I know the importance of the core data sheet because, you know, that product is owned by the company and that's their best thinking. And then the parallels between the core data sheet and the European label.

And so my guide for what should be included in the U.S. label is what I saw that I thought was appropriate in the core data sheet as well as what I saw in parts of the European label.

Q. Okay. Come back to my question. What is the range that should be included in the U.S. label in terms of plasma

HARVEY

concentration?

MR. MOSKOW: You're asking for a specific number range?

MR. SCHMIDT: Uh-huh.

A. So I agree with what I saw in Dr. Temple's slides where he talked about 50 to 150. I could certainly understand if you wanted to have a cutoff of 200, I think, or 75 to 150 is another range. I would think you would want to do it based upon data. And some of the data I hope is available to do that. Some might not be to do it adequately in some of the subpopulations. So advancing age, there might not be adequate numbers. Certain patients with certain ranges of renal function, some of the comorbidities, previous GI bleeds, those ranges would need to be based upon data. But I think we certainly have a series of proposals which then need to be studied.

Q. Well, you've looked -- you purport to have looked at the BI documents on this issue; right?

A. Yes.

Q. You purport to have done a complete

HARVEY

review of the data as it exists; right?

A. Yes.

Q. What should the number be? What should it say in the label in terms of a range?

A. Well, whether it be 50 to 150 or 75 to 150, that certainly is better than what it is now, which is no range.

Q. I'm not asking for what's better; I'm asking what should it be. And here's why I ask. Let's do a little exercise. On page 27 of your report you cite a document that gives a range of 50 to 150.

A. Correct.

Q. Right? And do you know how many Pradaxa patients in the RE-LY study where plasma concentration was measured fell outside that range?

A. I don't have the exact numbers, but there was discussion about a third that might have fallen in the -- outside the range.

Q. Okay. Another number you cite, going back to 25, page 25, is you talk about the 10th and 90th percentiles --

A. Correct.

HARVEY

Q. -- from the RE-LY study. Do you see that?

A. Uh-huh.

Q. And just so I have it, what that means is if you put everyone on a chart in terms of what their concentration was, you looked at where the 10th percentage of people were and then all the way up to what the 90th percentage of people were; right?

A. Correct.

Q. And do you remember what those numbers are? What was the 10th percentile in terms of the blood levels and what was the 90th percentile?

A. No, I don't.

Q. Do you know if the 10th was above or below 50?

A. The -- based upon the data I remember, the blood level of 50, below which strokes, you know, increased significantly, and so it would be in that range of 50.

Q. Am I correct in understanding your answer right now that you should not go below 50 nanograms per milliliter in terms of stroke

HARVEY

risk?

MR. MOSKOW: Objection to form.

A. All of the information I've seen, there is general agreement that going below 50 increases your stroke risk.

Q. Okay. So to come back to my question, should you avoid going below 50?

A. Yes.

Q. And if you look at your report where you talk about the fact that 10 percent is a potential cut point for an increased risk of stroke; is that correct?

MR. MOSKOW: Objection to form.

A. Yes.

Q. Do you know what -- if the 10th percentile is above or below 50?

A. As -- if I could look at specific information, but my recollection is that it's in that area.

Q. Am I correct in understanding your report to say you would be okay if the recommendation was to stay within the 10th and 90th percentile?

MR. MOSKOW: Objection to form,

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mischaracterizes the document.

A. I think what I'm discussing is, you know, I'm discussing why the one-size-fits-all approach doesn't take certain things into consideration. I don't think I'm making a specific proposal; I'm just saying why the current paradigm of no monitoring, one size fits all, doesn't take into consideration some of these factors.

Q. But you do say below -- the 10th or below is a subtherapeutic dose where you have increased risk of stroke; correct?

A. The -- I think there is general agreement that a drug level of 50 -- below 50 is subtherapeutic, and if that corresponds to the 10th percentile, then that's consistent.

Q. Well, that's what I'm asking you.

A. I've not memorized the numbers.

Q. Is, as your report says, a dose below the 10th percentile subtherapeutic? Do you stand by that statement in your report?

A. I think as I read the report, I'm saying one size does not fit all. And that approach ignores the data that 20 percent of

HARVEY

the population received either a dose that was too high or too low.

Q. Right. So is below the 10th too low?

A. That's what I say in my report and I agree with that.

Q. Is above the 90th too high?

A. Yes.

Q. And is between 10 and 90 okay?

A. Well, we're talking about in general --

Q. Yes.

A. -- and so --

Q. In general is between 10 and 90 okay?

A. But that's not what I'm saying.

Q. That's what I'm asking. In general is between 10 and 90 okay?

A. And we're not talking about specific subpopulations that are at high risk?

Q. Right.

A. If I can clarify, what I was --

Q. Can you just answer my question? In general is between 10 and 90 okay?

MR. MOSKOW: Objection. If you are able to answer, you should. If you need

HARVEY

more information, you should ask for it.

A. I need more information because that's an oversimplification.

Q. You understand that the 10th and 90th percentiles are arbitrary points along a data spectrum; right?

A. Yes.

Q. For example, you could just as easily say let's define it according to the 5th to 95th percentile or the 15th to 85th percentile; right?

A. That's correct.

Q. And that's true in terms of the data; there's nothing special about either the 10th percentile or the 90th percentile in terms of the data, is there?

A. That's correct.

Q. For example, if you go from the 85th to the 90th percentile versus the 90th to the 95th percentile, in both increments you see an increased risk of bleeding, but it increases at the same rate; right?

A. Yes.

Q. There's no -- if you were to say

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above this level in terms of the percentile or in terms of the blood concentration, there's an increased risk of bleed, you could literally say that as to any blood level; right?

A. That's where you lost me.

Q. Okay. The --

A. Because the --

Q. The --

A. -- current paradigm --

Q. Let me --

A. -- is 0 --

Q. Let me --

A. -- to 90th --

Q. -- try to --

A. -- percentile, or 0 to 100th percentile.

Q. Fair enough. Let me try to ask the question more precisely.

You refer to this -- the statements in company documents where they talk about an increased risk of bleeding above 200 nanograms per milliliter; correct?

A. Correct.

Q. And that is a true statement;

HARVEY

correct?

A. Yes.

Q. It would be equally true to make that statement about any blood concentration level; correct?

MR. MOSKOW: Objection to form.

A. So there is evidence that above 200 increases your risk of bleeding, so I don't follow that --

Q. Okay.

A. Because it's an increased risk for 200 and above that has been identified within the company as well as in certain publications. But I don't follow the second part of your question.

Q. Would it be a true statement to say above 50 nanograms there's an increased risk of bleeding?

A. Increased risk over?

Q. Below 50.

A. That would be an odd comparison but that would be a true statement if you were making -- with that -- with that -- if you are using 50 above and below, then that would be a

HARVEY

true statement.

Q. Okay. Is it true to say there's an increased risk of bleeding above 100 nanograms per milliliter?

A. Well, there is data to support that in the Reilly paper, figure 2, where with increasing dose there's increasing risk.

Q. Right. As your plasma concentration increases your bleeding risk increases; right?

A. That's correct.

Q. So you could make that statement, to come back to my first question, there's an increased risk of bleeding above 200 nanograms per milliliter. You could make that statement about any level because as you go up any level, your bleeding increases; right?

A. And that's on the risk side, that's correct.

Q. Right. But you also need to consider the stroke benefit side; right?

A. That's correct.

Q. Because you would agree with me that there is no plasma concentration level you can identify where there is not some increased

HARVEY

stroke benefit above the lower level?

MR. MOSKOW: Objection to form.

A. So the curves are different. And if you are trying to have benefit/risk, you would want to look at both curves on the same graph, which is what figure 2 is in the Reilly article. And if the risk of bleeding goes up at a faster rate than any corresponding reduction in stroke, then that's not improving the benefit/risk ratio.

Q. Move to strike as nonresponsive. Is it true that according to the data you have seen, as you go up each level in terms of blood concentration, there is always some increased stroke protection?

MR. MOSKOW: Objection to form, asked and answered.

A. Stroke protection, I would say no, because there's a part of the curve where it appears to level off.

Q. So is it your testimony that at the high end, the stroke protection completely levels off? Is that your testimony under oath?

MR. MOSKOW: Objection to form.

HARVEY

A. I'm saying as I look at figure 2, it appears to be leveling off, but it's -- I can't say that it's flat.

Q. Does it ever become flat? Have you tried to quantify that?

A. No, I have not. I've looked at the graph and it looks relatively flat, but I haven't expanded it and looked at the scale.

Q. For example, do you know who Dr. Baruch is?

A. Yes.

Q. He's one of the plaintiff experts; right? Correct?

A. Yes.

Q. Unlike you he's a cardiologist; right?

A. Uh-huh.

Q. Yes?

A. That's my understanding.

MR. MOSKOW: He's just saying you need to answer audibly. So "uh-huh" doesn't work on the record.

A. Yes, that's my understanding.

Q. And unlike you, he actually has

HARVEY

prescribed Pradaxa in the real world?

A. That's what I understand.

Q. And did you know -- did you review his testimony?

A. Yes, I did.

Q. Did you see that he had actually quantified the stroke benefit that you get at higher levels of the curve?

A. Yeah, he did that analysis, yes.

Q. And did you see from his analysis that whether the curve flattens out, gets flatter or not, there is always an improvement in stroke benefit as you increase concentration? Did you see --

A. That was his characterization of it.

Q. Do you have any basis to disagree with the factual proposition that as plasma concentration increases, there is always some additional stroke benefit?

Do you have any reason factually to disagree with that proposition?

MR. MOSKOW: Objection to form.

A. In a regulatory sense, we never say always. It's only within the data. And when I

HARVEY

look at figure 2, it looks relatively flat.

Q. Okay. Not --

A. So what I'm saying is not inconsistent with what you've just outlined.

Q. Move to strike as nonresponsive. I'm asserting factually -- Dr. Baruch happens to agree with me -- that as concentration increases on the curve, there is always some additional stroke benefit.

Do you disagree with that factual proposition?

MR. MOSKOW: Objection to form.

A. What I disagree with is the extent of which that data demonstrates that. Since I don't believe -- I would need to see what doses were studied. You know, where is the extrapolation? Where's the interpolation? How many patients were studied?

There's a flattening of the curve is what I've observed, which doesn't necessarily mean it goes to a delta of zero.

Q. Are you done with your answer, sir?

A. Yes, I am.

Q. Let me try my question again. I

HARVEY

thought it was clear but I'll flag it. It's just a yes or no question, or I don't know. Yes or no or I don't know: Do you agree with the factual proposition that as plasma concentration increases, there is always some additional stroke benefit?

MR. MOSKOW: Objection to form.

A. I disagree with the word "always."

Q. Okay. Do you disagree with me that -- strike that.

Do you have any basis to disagree with the factual assertion that as the plasma concentration of Pradaxa increases, the stroke rate continuously decreases --

MR. MOSKOW: Objection to form.

Q. -- according to the data we have?

A. According to the data, there is a diminishing corresponding reduction in stroke rate. I agree with that.

Q. The stroke rate continuously decreases. It never stops decreasing as you increase in plasma concentration?

MR. MOSKOW: Object.

A. "Never" and "always" I can't agree

HARVEY

with.

Q. Does the stroke benefit ever stop as you increase with plasma concentration?

MR. MOSKOW: Objection to form.

Q. Yes or no or you don't know?

A. I don't know.

Q. Have you attempted to quantify in any way how the stroke benefit or the stroke rate changes when you go from, say, 200 nanograms per milliliter to 250 to 300? Have you tried to quantify any of that other than just eyeballing a curve?

A. I think it would be ill advised to study that in a real patient, but no, I haven't quantified that.

Q. There is data from which you can quantify that, though; right Dr. Baruch has tried to do that.

A. I understand that, and that's his area of expertise, and my thinking doesn't contradict that.

Q. You agree with Dr. Baruch then on the continuing stroke benefit above 200 nanograms per milliliter?

HARVEY

MR. MOSKOW: Objection to form.

A. I agree with his opinion. I'm just providing my regulatory perspective that it's going to be based upon the data, and terms like "always" and "never" make me uncomfortable.

Q. You agree with Dr. Baruch that the stroke benefit from Pradaxa continues to increase even as you go beyond 200 nanograms per milliliter?

A. Yes, I do.

Q. And you agree with him that that is clinically significant?

MR. MOSKOW: Objection to form, mischaracterizes the testimony.

A. I agree with his testimony as I've read it in the transcript.

Q. Did you see where he said it's clinically significant, the improvement that you get in stroke rate, even as you go above 200?

MR. MOSKOW: Objection to form.

THE WITNESS: There's been an objection to the characterization of the testimony.

HARVEY

MR. SCHMIDT: Okay, then I'm going to put an objection on the record right now. That's a coaching objection. The witness has just said on the record he has been coached. I'm not going to have a fight about it because you're -- you're an honest defender and --

MR. MOSKOW: It's not -- it's not --

MR. SCHMIDT: I think it was a --

MR. MOSKOW: -- what I meant --

MR. SCHMIDT: -- one-time thing, but --

MR. MOSKOW: -- to do, but I --

A. It's not my -- my statement that I've memorized the expert testimony of another expert, and to question whether or not I'm remembering his testimony is outside the scope of my report and my expertise.

Q. Do you know whether there is a clinical, meaningful clinical benefit in stroke protection when you go above 200 nanograms per milliliter?

A. I do not know that.

HARVEY

Q. Do you know if there's a meaningful clinical benefit when you go above 300 nanograms per milliliter?

A. I do not know that.

Q. All right. So let's go back to the numbers. We've now talked -- on page 27 you cited a document referring to 50 to 150.

Do you remember that?

A. Yes, I do.

Q. On page 25 you cited a document -- or you discussed the 10th to 90th percentile; correct?

A. Yes, I did.

Q. On page 37 you cite a document talking about 40th -- 40 to 200 nanograms per milliliter?

A. Which page was that?

Q. I'm sorry. Page 37. It's the Connolly email down at the bottom.

Do you see that?

A. I see there is a very good reason never to go above 200.

Q. Do you see where he says there's a rough plasma concentration range for

HARVEY

optimization of efficacy and safety in a range of 40 to 200?

A. Yes, I do.

Q. And that disagrees with your number; right? Is Dr. Connolly wrong in saying you can go down to 40?

MR. MOSKOW: Objection to form, misstates the document. Objection to form.

A. All of the different ranges that I'm citing are based upon the work of those individuals. They're all similar in their desire to have some sort of range, which is better than where we are now with the U.S. label, where there's no range at all.

Q. Move to strike as nonresponsive. Is Dr. Connolly incorrect in your view in saying that your plasma concentration can be as low as 40? Yes or no --

MR. MOSKOW: Objection to form.

Q. -- or you don't know?

A. I don't see 40 versus 50, when he's speculating on potential ranges, as inconsistent or mutually exclusive.

HARVEY

Q. Do you view this email as his speculation on potential ranges, to use the word you just used?

A. He's commenting on a draft document.

Q. Move to strike as nonresponsive.

A. I just read it from my report.

Q. Do you remember what my question was?

A. Do you think it was speculation?

Q. Yeah, that's the word you used. You said I don't see 40 versus 50, when he's speculating on potential ranges.

A. Okay.

Q. Do you understand -- let me finish my question.

A. I'm going to turn the page because I actually answered it in my report.

Q. Do you understand him to be speculating on the potential ranges? Yes or no.

A. Am I allowed to turn the page and quote the rest of it, saying "of events, but somewhere around 40 to 50 seemed prudent."

Q. Under --

A. He actually said it was 40 to 50 --

HARVEY

Q. Sir --

A. -- so to say 40 versus 50 is a -- a false distinction.

Q. You are not answering my question at all, respectfully, sir. You're allowed to look at whatever you want to look at.

A. Okay.

Q. But I have to ask you to answer my question. My question was not about 40 to 50. My question was simply do you understand him -- two minutes ago you used the word "speculating." You said, "I don't see 40 versus 50 when he's speculating on potential ranges." I was just asking you, do you understand this email to be him speculating on ranges? Yes or no.

A. In the quote, he talks about 40 to 200, and then later in the same quote, "but somehow around 40 to 50 seems prudent." So that's to me is not a definitive recommendation, but he is seeking to find a range, which is then something that needs to be tested.

Q. Can you answer my question now? Is

HARVEY

that word you used two minutes ago, "speculating," accurate for what he's doing in this email? Yes or no. Is he speculating?

A. Did you want to give me a definition of "speculation"?

Q. The same one you used two minutes ago.

A. Okay. It's -- that's how I characterized it. Since he does mention 40 and then he says 40 to 50.

Q. It's a fair characterization of his email that he's speculating about a range; correct?

A. Yes.

Q. And what was his final opinion on what the range should be?

Let me just take a step back. I'll withdraw that question. You understand that Dr. Connolly along with Dr. Reilly, to whom this email was sent, did a great deal of hard thinking about what a range might be; right?

A. Yes.

Q. What was Dr. Connolly's -- having done that hard thinking, what was his final

HARVEY

view when he was done speculating and came to his final view as to what an appropriate range was, if any?

MR. MOSKOW: Objection to form.

A. I'm reluctant to give you an answer because there's no simple answer because they go on -- we go on to talk about risk factors and age and creatinine clearance.

Q. Let me be sure -- I think you might be answering a different question than I'm asking. I'm focused on Dr. Connolly specifically. What was his final view after he had speculated and discussed and thought through the data as to whether there was an optimal plasma concentration range and, if so, what it was? Do you know? Do you know what his final opinion on the matter was?

A. I would need to see the paper.

Q. Which paper would you need to see?

A. The paper we're referring to in the final publication version of the above paper.

Q. Okay. You understand that to be the --

A. The Reilly paper from 2014.

HARVEY

Q. You understand that to reflect Dr. Connolly's final views on this issue?

MR. MOSKOW: Objection to form.

A. I'm asking to see the paper so I can answer that.

Q. Do you know if Dr. Connolly's an author on that paper?

A. I'm waiting for the paper.

Q. We're getting it. Do you know if he's an author on that paper?

MR. MOSKOW: Objection.

A. I'm waiting for the paper.

Q. Without seeing the paper do you know if Dr. Connolly was an author on that paper?

A. I'm waiting for the paper.

Q. Can you answer my question, sir? If you are literally refusing right now to answer my questions, we will have to go to the judge on that.

MR. MOSKOW: Objection.

Q. Do you know?

MR. MOSKOW: Just show him the paper.

Q. Do you know if Dr. Connolly is an

HARVEY
author on the 2014 Reilly paper? Are you refusing to answer my question, sir?
A. No, I'm not refusing to answer. I've asked for the -- a paper, which I think is a legitimate request, and you're refusing to give it to me.
Q. I'm not refusing to give it to you. I'm asking if you know without looking at it.
Do you know without looking at it?
A. No, I don't.
Q. Okay.
(Harvey Exhibit No. 8 was marked for identification.)
BY MR. SCHMIDT:
Q. It's marked as Exhibit 8. Do you see that this is the paper that you referenced from 2014, what's sometimes called the exposure paper?
A. Yes.
Q. If you look, do you see that Dr. Connolly is, in fact, an author on this paper?
A. Yes, I do.
Q. And let's look at the final

HARVEY
conclusion of this paper. Look with me if you would at page 328. I'm going to read into the record the second-to-last sentence of this article. Do you see where it says: "There is no single plasma concentration range that provides optimal risk/benefit for all patients"?
Did I read that correctly?
A. Yes, you did.
Q. Do you understand that to be Dr. Connolly's final conclusion, after he's done speculating, after he's done talking about it, after he's done considering the data?
MR. MOSKOW: Objection to form.
A. But the sentence you just read was for all patients. And in my report, I cite that there are issues with old age, reduced creatinine clearance, low body weight, and that better outcomes might be achieved by adjusting dose. So yes, it's a true statement for all patients, there's no single range, but it negates his comments on those special populations that are at increased risk.
Q. Move to strike as nonresponsive. Do

HARVEY
you agree with the statement in this paper that there is no single plasma concentration range that provides optimal benefit/risk for all patients? Is that a true statement as you understand it?
MR. MOSKOW: Objection to form.
A. As written, I agree.
Q. Okay. Do you understand that to be Dr. Connolly's final view on that issue?
MR. MOSKOW: Objection to form.
A. Given the limitations that I said about all patients, not specific high risk populations.
Q. Yes? That's his final view --
MR. MOSKOW: Objection to form.
Q. -- subject to those limitations?
Let me take a step back and reask the question. Have you ever seen Dr. Connolly refer to specific plasma concentration ranges for high-risk patients? Did he do that in the email that you cite on page 37 of your report?
A. There was the discussion that we -- we've already had about the 40 to 200. It's -- about not going above 200, and that the 40 and

HARVEY
50 seems to be prudent as the lower boundary.
Q. Was that general or related to specific populations?
A. The specific populations came later.
Q. Okay.
A. That was in general then, to answer your question.
Q. And his ultimate conclusion, having speculated about 40 to 200, his ultimate conclusion was there is no single plasma concentration range; correct?
MR. MOSKOW: Objection to form.
A. That's what he states in his article in 2014.
Q. You give various other numbers in your report. We've talked about 50 to 150, we've talked about 10th to 90th percentile, we've talked about 40 to 200. If you look at page 41 of your report, you reference the pediatric studies that we've already touched on which are 50 to 250.
Do you see that?
A. Yes.
Q. Is that an appropriate range in your

HARVEY

view?

A. Based upon what I've read, I would be uncomfortable with going up to 250. But children are different from adults in how they metabolize things, and I would hope that there would be some adjustment for creatinine clearance. Although kidney -- you know, renal insufficiency is unusual in children, it's not impossible.

Q. Would you be -- you understand that the 50 to 250 was based on adult data, not child data; right?

A. It's my understanding that it was data that was generated not using children, that's correct.

Q. Would you be comfortable having adults dose 50 to 250?

MR. MOSKOW: Objection to form.

A. Given that experts have been quoted saying there's no good reason to go above 200, and given, you know, the figure 2 from the Reilly paper where you don't see much benefit above 200 on the two curves, I don't -- I wouldn't see the utility of going above 200.

HARVEY

Q. Let's look at figure 2 from the Reilly paper. It's Exhibit 8. And this is the curve that you have referenced several times; correct?

A. Yes.

Q. So we have it, there's one curve that shows a dotted line corresponding to bleed.

Do you see that?

A. Yes, I do.

Q. And do you see that that tends to flatten out as you get higher plasma concentrations? It increases less steeply?

A. It -- the rate of slope changes. I wouldn't say it's flattening out.

Q. And there's a dotted line with gray lines around it.

Do you see that?

A. Yes.

Q. What does the dotted line reflect and what do the gray lines reflect?

A. So we're looking at increasing concentration and the event probability.

Q. Yeah. And what's the difference -- what's the dotted line signify and what does

HARVEY

the gray line signify, the gray shading area?

A. So you've got the data and then you've got the range, the range.

Q. Is this modeled data or actual data?

A. Well, I object to the term "actual" distinguishing data between modeling, given what we have been talking about.

Q. The way this works, you're a witness, you can't object. They can object.

A. Okay.

Q. So is this --

MS. PRESBY: I object.

A. I question -- given the --

Q. Let me reask the question --

A. -- our previous discussions --

Q. -- and see if I can meet your concern. Is this literal patient data or is this modeling from patient data? Do you know?

A. It's my -- it's based upon actual data, and then the gray area is the 10th to the 90th percentile.

Q. You read that on the page.

A. No, because I quoted it in my report.

Q. Is it modeled? Is there modeling

HARVEY

involved in this?

A. There might be some modeling involved.

Q. Do you know?

A. But it's based upon the actual data, to use your term.

Q. Do you know if there's modeling involved? Yes or no. Or you don't know.

A. I don't know.

Q. Okay. And you said that there's a 10th to 90th percentile. So just to take an example -- and what I'm going to ask you to do is if you could look at where it has 250 nanograms per milliliter.

Do you see that?

A. Uh-huh.

Q. And just because you've got a copy of the exhibit -- I'll do it actually if you want. Do you mind passing me yours? Do you see how I've drawn a line on the stroke curve above -- if you guys need to take a look at that, obviously do -- above the 250 marker? Through the gray area?

A. Yes, I do.

HARVEY

Q. Does that mean that we know that the stroke benefit could be anywhere in that range?

MR. MOSKOW: Objection to form.

A. By definition of a 10th to 90th percentile, then yes.

Q. So it could be the very bottom of the range; it could be the high end of the range?

A. Correct.

Q. And do you see where it says "calculated for a 72-year-old male"?

A. Yes.

Q. How does this apply to a 72-year-old female?

A. I don't know.

Q. How does it apply to an 80-year-old?

A. I do not know.

Q. Have you seen curves like this for 80-year-olds or for females?

A. No, I don't remember if I have.

Q. And sticking with the stroke, if you look at the left-hand side of the graph it says "event probability."

A. Uh-huh.

Q. This is the percentage chance of

HARVEY

someone -- this is an attempt to model the percentage chance of someone having a stroke in those groups; correct?

MR. MOSKOW: Objection to form.

Q. At those plasma concentration levels?

MR. MOSKOW: Objection to form.

Q. Correct?

A. Can you repeat the question?

Q. Sure. What this is attempting to do is it's an attempt to predict the percentage chance that someone at a given plasma concentration level will have a stroke; right?

MR. MOSKOW: Objection to form, mischaracterizes the document.

MR. SCHMIDT: I'm going to ask you not to make that mischaracterization objection, given what the witness has done.

MR. MOSKOW: Well, you're talking about one half of an X-Y chart, so --

MR. SCHMIDT: That's what I'm --

MR. MOSKOW: -- you're mischaracterizing.

MR. SCHMIDT: I referred to both

HARVEY

the plasma concentration, which is --

MR. MOSKOW: And you talked about one of the -- one risk factor.

MR. SCHMIDT: Yeah, stroke. That's my question.

MR. MOSKOW: But that's not what the chart reflects. That's my --

MR. SCHMIDT: You can't coach him on it, and you have coached him already.

MR. MOSKOW: Which is why I said mischaracterization as opposed to saying anything more.

MR. SCHMIDT: "Mischaracterizing" is coaching this witness and he's demonstrated that. Doctor, let me try to reask the question to avoid the objection.

BY MR. SCHMIDT:

Q. Do you see that this reports predicted stroke data?

MR. MOSKOW: Objection to form.

Q. Yes or no.

MR. MOSKOW: You can answer if you're able.

HARVEY

A. Can you repeat the question?

Q. Do you see that this reports predictions for stroke data based on different plasma concentrations?

MR. MOSKOW: Objection to form. You can answer if you're able.

A. You're talking about figure 2?

Q. That's what we have been talking about for the past ten minutes, yes, sir.

A. I understand that. I just wanted to make sure we hadn't changed. Can we take a break?

Q. Not in the middle of a question.

MR. MOSKOW: You have to answer his questions if you're able.

THE WITNESS: Okay. Why don't you ask the question one more time?

Q. Okay. Do you see that figure 2 reports predictions for stroke data based on different plasma concentrations?

MR. MOSKOW: Objection to form.

A. So it's ischemic stroke/SEE versus trough plasma concentration --

Q. It report --

HARVEY

A. -- of the drug.

Q. It reports a prediction about the percentage chance -- the event probability for strokes and SEE at different plasma concentrations; correct?

MR. MOSKOW: Objection to form.

A. That's -- that appears to be what it does, yes.

Q. And what it shows is that the event probability decreases as the plasma concentration increases; correct?

MR. MOSKOW: Objection to form.

A. Yes.

Q. And within -- at every point in the plasma concentration there's a range of how much it decreases by from the 10th to the 90th percentile; right?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. And the rate that it's showing us is the absolute -- when it says "event probability" -- do you see that on the left-hand side?

A. Yes.

HARVEY

Q. You understand that to be just how common are the strokes predicted to be; correct?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. So, for example, you see where it says 2, 4, 6, 8?

A. Yes.

Q. That would be predicting a stroke rate of 2, 4, 6, 8 percent; correct?

MR. MOSKOW: Objection to form.

A. That's my understanding.

Q. Now, you understand that different patients have -- if they don't receive anticoagulant treatment, different patients have different stroke rates; right? Different stroke risks; correct?

A. Yes.

Q. For example, this is a 72-year-old male. An older patient is more likely to have a higher stroke risk?

A. Yes.

Q. A patient with poor renal function is more likely to have a higher stroke risk?

HARVEY

A. Correct.

Q. And both of those patients, older patients and patients with higher renal functions, who have higher stroke risks if they don't take medication, if they do take Pradaxa, they're likely to have higher plasma concentration levels; correct?

MR. MOSKOW: Objection to form.

Q. Generally speaking.

A. Can you repeat that, please?

Q. Sure. It was a complicated question. Let me break it down. On average, older patients who take Pradaxa are likely to have higher plasma concentration levels?

MS. PRESBY: Objection.

Q. Let me withdraw the question.

Do you know -- if you look at the higher -- let me strike it. I'll move on.

The other numbers that you report in -- let me show you one other set of numbers. We've talked about 50 to 250, we've talked about 40 to 200, we've talked about 50 to 250.

Do you remember that?

A. Yes.

HARVEY

Q. Can you tell me one of those is the right range for all patients?

A. No, I can't.

Q. Can you tell me one of those is the right range -- you talked about high-risk patients. Can you tell me one of those is the right range for a defined high-risk patient group?

A. Based upon the information I've reviewed, I think there's evidence to support the choice of 50 to 150 for high-risk patients.

Q. And how do you define high-risk patients?

A. Those of advancing age, those with diminished kidney function, those with a history of previous GI bleed or other bleeding abnormalities, those on certain medications.

Q. What age would qualify for that range?

A. Well, I would have to look at the specific data, and there -- you know, there would actually have to be more data generated, which has not been done. And whether it be 75 or above or 80 or above, but I think there's

HARVEY

evidence of choosing 75, which others have.

Q. Based on the data that exists that you have seen, can you tell me -- you said generally there's no -- there's no range for all patients. Based on the data you have seen, can you tell me that there's a specific age group that should have a specific range of 50 to 150?

MR. MOSKOW: Objection to form. You can answer.

A. So I also put weight on the company's core data sheet and the information that went into that.

Q. Move to strike as nonresponsive.

A. Okay.

Q. Can you tell me a specific age group that should be subject to a plasma concentration range of 50 to 150 or any other specific range?

A. I would say as a starting proposal, 75 and above. And based -- and then you would need to go through the data, and where the data is inadequate, it means there needs to be new data generated.

HARVEY

Q. Okay. You say starting proposal; I want your final view. Should there be a warning that patients 75 and above should be monitored to stay within a range of 75 to 150? Yes or no.

MR. MOSKOW: Objection to form.

A. I believe I've seen enough to advocate that position, yes.

Q. You believe that should be the labeling? I don't want advocacy; I want your expert opinion. Should the label tell doctors if your patient is 75 or above --

A. But that's -- that's not --

Q. Let me finish the question.

MR. MOSKOW: Let him finish the question.

Q. Should the label tell doctors that if a patient is 75 or above they should be monitored to be kept within a specific plasma concentration range?

MR. MOSKOW: Objection to form.

A. So that would be one recommendation, yes.

Q. Okay. And that plasma concentration

HARVEY

range would be 50 to 150?

A. That would be what I would advocate.

Q. Would there be any other age-based labeling recommendations?

A. Not age-based. There would be --

Q. I'm going to go through the other ones. The next one you mentioned is diminished kidney function.

A. Correct.

Q. That's renal function?

A. Yes.

Q. Would that be a creatinine clearance measure?

A. Yes.

Q. What would be your recommendation there specifically in terms of what would be the cut point and what would be the range?

A. Well, I agree with what I've read in the European label and the core data sheet.

Q. Which say nothing about renal function and an optimal plasma concentration based on renal function.

MR. MOSKOW: Objection to form.

A. Do I have the core data sheet?

HARVEY

MS. PRESBY: I don't know that there's a question pending.

Q. We'll go back to my prior question, which is what would your specific recommendation be for a specific plasma concentration range based on renal function?

A. I would not make a specific recommendation. I would recommend that it would be based upon kidney function and then leave the specifics to the renal experts.

Q. Okay. There's no number you can give me, is there?

A. In my review I've seen others propose numbers that look -- look like they certainly would be a good starting point.

Q. And what are those numbers? Because I've not seen those.

MS. PRESBY: Objection, form.

A. Well, I have found some of the information, but I want to be complete. There is -- in the company core data sheet there is discussion about renal function in several different contexts, so I guess I'm confused by your statement that you haven't seen it.

HARVEY

Q. Let me go back to what I said. Have you seen it discussed in the context of specific plasma concentrations?

A. Table 13.

Q. Okay. What else?

A. And then --

Q. Actually, you know, my question is not what is it the core data sheet says. I started writing on a sheet what I'm trying to understand from you, so I've written down 75 years, 50 to 150 nanograms per milliliter. That's what we talked about five minutes ago.

A. Uh-huh.

Q. What I'd like you to tell me is what if any specific plasma concentration would you recommend based on renal function?

A. Well, renal function, if someone has a poor renal function, they can go higher than that 150 range at a lower dose. So it's not that you would necessarily have to change the range. It's that with poor renal function you're going to get a higher plasma concentration at a different dose.

Q. Let me try it this way. You

HARVEY

recognize that the label already recommends testing for renal function and adjusting dose if there's impaired renal function; right?

MR. MOSKOW: Objection to form.

A. I understand that in the U.S. label there's a 150-milligram dose and not a 110-milligram dose, so -- that's not the case in Europe. Why don't you repeat the question and I'll --

Q. I'll move to strike that as nonresponsive. You recognize that the label already recommends testing for renal function and adjusting dose if there's impaired renal function. True?

MR. MOSKOW: Objection to form.

A. There is some information in the current label about renal function, that's correct.

Q. Move to strike as nonresponsive. Does the label recommend monitoring renal function?

A. Yes.

Q. Does it recommend adjusting dose if there is impaired renal function?

HARVEY

A. Yes.

MR. MOSKOW: Objection to form.

Q. And are you recommending that there be any further dose adjustments based on plasma concentration tests of people who are known to have impaired renal function?

A. Yes.

Q. And so tell me what renal function you would do those tests at and what would be the range you were looking for.

A. And I guess what I'm having trouble is you're asking me to do that in 7 seconds when it hasn't been done in 7 years.

Q. Asking you to do it in 202.5 hours, sir.

MR. MOSKOW: Objection to form.

A. Making specific recommendations on renal ranges is not part of the purview of what I did as a regulatory consultant.

Q. So maybe that answers my question. Do you have a specific renal function level at which you would recommend testing blood concentration levels to hit a target range?

A. No, I don't.

HARVEY

Q. Let me go back to the other two and then we'll break. You mentioned patients who have a prior bleed as being another risk group.

Do you remember that?

A. Yes, I do.

Q. Do you have a specific recommendation for patients who have a prior bleed in terms of how to identify such patients to test their blood levels and what their range should be?

MR. MOSKOW: Objection to form.

A. Patients -- I mean, based upon my experience as well as my understanding of the literature is patients who have had a previous GI bleed are at increased risk for another GI bleed, and therefore the current label doesn't adequately address that concern. Dosing 50 to 150 would be a better benefit to risk than it currently is in the U.S. And given the risk factors of the individual patient if they've had a significant GI bleed, let's say, it may be that Pradaxa may not be right for them under the current no-monitoring paradigm.

Q. Move to strike as nonresponsive. Do you have a specific recommendation that certain

HARVEY

groups of patients who have had a prior bleed should have their blood tested before they use Pradaxa or while they're using Pradaxa to ensure that they remain within a specific therapeutic range?

MR. MOSKOW: Objection to form.

Q. Yes or no?

A. Yes.

Q. Okay. And what is the patient criteria that puts them in this category where they would be tested?

A. If a patient has had a previous GI bleed.

Q. Any GI bleed?

A. Any GI bleed.

Q. Whether it's related to an anticoagulant or not?

A. Doesn't matter if it's related to an anticoagulant. A lesion in the GI tract that's there has an increased chance of bleeding in the presence of anticoagulants.

Q. So I've written down "prior GI bleed." What would be the range you would be looking to keep that patient in?

HARVEY

A. I would have to look at the data.

Q. Okay. What's your best answer right now?

A. It would be something less than 50 to 150. It might be 50 to 100, which some have suggested in the literature.

Q. So I just wrote less than 50 to 150, maybe 50 to 100. Is that a fair summary of what you just told me?

A. No.

Q. Okay. How is that wrong?

A. It would be -- I didn't say less than 50 to 150 because you could imply I'm saying less than 50.

Q. I thought you meant narrower than --

A. Yes, so I --

Q. I'll change that to "narrower." Is that fair?

A. Yes.

Q. Okay.

A. Which is -- then I gave specifics of 50 to 100.

Q. Right. Maybe 50 to 100 I think is what you said.

HARVEY

A. Correct.

Q. So -- let me cover the third category. You said there's certain medications where people should be tested for optimal range. What are those medications?

A. Well, the one that's --

Q. Actually, I apologize. Are there certain medications where you believe -- because I'm not sure you did say that. I think I misstated what you said. So let me be sure I understand. Are there certain medications where you believe patients taking those medications while they're using Pradaxa should have their Pradaxa blood levels checked to make sure they fall in a certain range?

A. Yes.

Q. So let me ask, what are those medications?

A. Well, I don't have a comprehensive list. There's always been a concern about verapamil.

Q. You're going to have to help me spell that.

A. It's in the European label.

HARVEY

Q. How do you spell it?

A. V-E-R, verap -- V-E-R-A, verap --

Q. I-M-L?

A. I-M-L.

Q. I-M-I-L?

A. Yeah.

Q. We'll be together in misspelling it if we've misspelled it. Anything else?

A. I would have to go through and do a specific search in some of the databases. Now the pharmacies have the drug-drug interactions and contraindications and others.

Q. In your 200 hours of work on this case did you identify any ones other than verapamil where you believe patients taking that in addition to Pradaxa should have their blood checked?

A. I didn't go into the specifics of which drugs.

Q. For verapamil, what would be the target range for those patients?

A. I would defer to others on that.

Q. So here's what I was doing, then we can break for lunch. I'm going to mark this as

HARVEY

an exhibit. I was trying to -- helps me to be really concrete. I was trying to understand the instances where you believed something about the patient justified testing their blood levels to make sure that they fell within a certain range. And I've written down the three instances where you had a specific opinion on that point, along with what you told me about their blood ranges. Is that -- the blood ranges they should be aiming for. Is that accurate?

MR. MOSKOW: Objection to form. You've actually talked about four; there are only three on the --

MR. SCHMIDT: He didn't have one for diminished kidney function. That's why I didn't put it on there.

MR. MOSKOW: No, he gave one.

A. I said based upon what I have been reading in the core data sheet and in the literature, but I wasn't going to give specifics.

Q. So for the ones where you can give specifics, have I correctly reported the

HARVEY

specific recommendations you're comfortable making regarding patient characteristics that would justify testing and specific test ranges?

MR. MOSKOW: Objection to form.

A. It's incomplete.

Q. Okay. What is it missing?

A. It's missing kidney function.

Q. Okay. So let's add it.

MR. SCHMIDT: Why don't we go ahead and mark this. Is this -- 10 is the next one? I'm going to mark this as Exhibit 10.

(Harvey Exhibit No. 10 was marked for identification.)

MR. MOSKOW: I need a copy.

BY MR. SCHMIDT:

Q. Let me ask you, can you write "kidney function" on there?

A. No, I'm not going to do that.

MR. MOSKOW: You can do that.

A. This is -- it's really very concerning because this is not intended to be a comprehensive review. It could be that with the second generation product all patients

HARVEY

might benefit from some sort of dose adjustment. And so to carve these out -- these are special interests, but it doesn't then give the rest of the population a free pass.

Q. Doctor, I'm entitled to know your opinions as best you have them sitting here right now.

A. Uh-huh.

Q. You having told me you're ready to go before a jury now. And that's all I'm trying to understand is the instances where you are comfortable sitting here right now and saying there's certain patient groups who should be monitored. And you've added renal function to the list that we have been talking about. Do you have a range for renal function or is it defer to others that you just wrote?

A. Defer to others.

Q. Okay. And I think where we got tripped up on renal function is can you write down the creatinine clearance level at which you would start monitoring those patients?

A. I would defer to others on that.

Q. So may I ask you to write "defer to

HARVEY

others" on level of renal function?

A. I think I just did.

Q. You did as to the blood concentration level, but I'm talking the left side, even as to what their renal function is. For example, you gave me a specific age; right? You gave me 75 years of age; right?

A. Yes.

Q. You didn't give me a specific renal function. Are you deferring to others as to what the specific renal function level would be before you would monitor?

MR. MOSKOW: Objection to form.

A. Yes.

Q. Okay. So recognizing that you may do -- that if you were to go do a further search you might identify additional groups, am I correct that Exhibit 10 reflects the groups that at this moment you are comfortable saying, with the level of specificity reflected on Exhibit 10, that these are the groups of patients who should be monitored and this is the blood level that you should be looking for?

MR. MOSKOW: Objection to form.

HARVEY

A. These are groups that are at increased risk and should be monitored, but there may be others that should also be tested and adjusted, and as information becomes available, it may be all patients might benefit from dose adjustment.

Q. Based on the information you have now, having done your 200-hour review, are there any patient groups other than the four identified on Exhibit 10 that you believe should be monitored?

MR. MOSKOW: Objection to form.

Q. Specific ones.

A. I would have to do a more in-depth dive on the data to see if that 75 years needs to be lowered.

Q. Okay. But you're not prepared to say it should be lowered now, are you?

A. No.

Q. Okay. So based on the review you've done, the 200 hours, are there any groups missing from Exhibit 10 who should be monitored to hit a specific blood concentration range when they use Pradaxa --

HARVEY

MR. MOSKOW: Objection to form.

Q. -- that you can point me to?

A. Once again, I mean, these are special populations that deserve special consideration but it doesn't then absolve the rest of the patients from not benefiting from some sort of dose adjustment.

Q. Well, you said before not everyone should be monitored, so I'm trying to understand who you think should be monitored.

MR. MOSKOW: Objection to form.

Q. You've identified for me on Exhibit 10 who you think, based on your review to date, should be monitored; correct?

A. No, because I made a distinction between monitoring and dose adjustment. Monitoring is -- I would assume, and you can correct me, that would be like the testing that's in Coumadin. We're not talking about that. We're talking about a patient who's put on a specific dose and then you measure a level to see what range they're in.

So I had made that distinction earlier on in my testimony, that I

HARVEY

differentiate between monitoring and dose adjustment testing.

Q. Let me see if I have your testimony. Does Exhibit 10 refer to patients who should be subject to routine monitoring or just an initial blood test with a dose adjustment?

A. These are patients that would benefit from initial dose adjustment, and as they advance in their disease, periodic testing.

Q. Should everybody have an initial dose adjustment who takes Pradaxa?

A. Given the number of bleeds that have been reported, the absolute number, I think that that would further enhance the benefit/risk of this drug.

Q. And so what should be the range that everybody should be dose adjusted to in terms of their plasma concentration?

A. I think there is evidence to support 50 to 150.

Q. That's what you would recommend?

A. That's what I would recommend.

Q. Okay. You would recommend that for every single patient?

HARVEY

A. No. I think we've -- we've said that if you had a previous GI bleed or are higher risk, then 50 to 100 may be more prudent.

Q. Okay. But every patient should have their blood levels checked once, and if they're in that range of 50 to 150, they're okay. If not, then they should have their dose adjusted?

A. Yes, but with the caveat that if somebody has renal dysfunction, they could worsen over time, so it makes sense you have to periodically check. And I don't have specific recommendations on what that should be. And a patient who's 75, who then becomes 80 or 85, then needs some monitoring -- you know, some testing as well as they progress, since bleeding risk does increase by age.

Q. So how often should patients get tested as they age and how often should they get tested based on renal function?

MR. MOSKOW: Objection to form.

A. I don't have a specific recommendation at this time. I -- if I was a consultant on this case, I could sit down and produce something, but this is not the best

HARVEY

environment to -- for me to create a development program. You know, the companies had years to do this and they haven't.

Q. They've come to their view, haven't they?

MR. MOSKOW: Objection to form.

Q. Correct?

A. Yes.

Q. And you're coming to a different view; right?

A. I'm coming to a different view.

Q. But you can't articulate what that view is in terms of --

A. The specifics.

Q. In terms of how often people should be tested; correct?

MR. MOSKOW: Objection to form.

A. Correct.

Q. And you can't articulate what that view is in terms of what the optimal plasma concentration rate is, can you?

MR. MOSKOW: Objection to form.

Q. Or have you settled on 50 to 150?

MR. MOSKOW: Objection to form.

HARVEY

A. There are a lot of questions in there. Which one should I answer?

Q. You can't articulate your view as to what the optimal plasma concentration range is, can you?

MR. MOSKOW: Objection to form.

A. I have mentioned 50 to 150 as a range, and then as you increase risk, that can be further narrowed.

Q. Okay. So is that your testimony, that it should be 50 to 150 for all patients, narrowed as you increase risk? The maximum range is 50 to 150 and it only gets smaller as you have risk factors?

A. I'm not -- I'm not discussing all patients. Part of my objection is that the company's policy was no testing, no monitoring for all patients. My position in my paper is that treatment needs to be individualized, and so if a certain physician in evaluating their patient, given the benefit/risk and all the details of the individual patient, believes that there should be a testing of drug levels, then I would certainly support that. And the

HARVEY

way that you phrased it, that would negate that opportunity.

Q. Should all patients have their blood levels tested at some point? Yes or no?

A. Yes.

Q. So you are advocating testing all patients?

A. Yes.

Q. What should be done with that information?

A. That's what we're discussing.

Q. Right. Should every patient be dose-adjusted so that they fall within 50 to 150?

MR. MOSKOW: Form.

Q. At a maximum.

A. As a guideline, yes. As a rule of thumb. And then the therapy then should be tailored to the individual based upon the physician or practitioner.

Q. So in your world -- I'm almost done. In your world, if a patient comes in, they should be tested, and if they're at 185, they should be dose adjusted to get within 50 and

HARVEY

150?

A. Yes.

Q. Has any regulator in the world agreed with that view?

MR. MOSKOW: Objection to form.

A. I don't know what every regulator in the world has said.

Q. Has any regulator required testing that you can point me to? Blood testing that you're talking about?

A. No.

Q. Has any regulator given a range of 50 to 150 that you know of that all patients should aim for?

A. Bob Temple has mentioned that on several occasions in his slide set.

Q. Has any regulator done that?

A. Bob Temple is a regulator.

Q. Has he directed a label change to have a range of 50 to 150?

MR. MOSKOW: As of today.

A. As of today, no.

Q. Is he a pretty senior FDA official?

A. He's a deputy center director.

HARVEY

Q. That's pretty senior; right? He's one of the most senior people at the FDA; right?

A. In Center for Drugs.

Q. And he's very well regarded; right?

A. Yes, he is.

Q. And he has the power, if he really believes something, to effect a label change; right?

MR. MOSKOW: Objection to form.

A. That's not how the process works. The process is that it's the division and the office -- it's the division that initiates these changes.

Q. Does he oversee the division?

A. Actually, he is an acting -- he has an acting title in the office, second to Ellis Unger, who is also one of the authors on the paper.

Q. So is that yes?

A. Can you ask your question again.

Q. Yes. Does he oversee the division responsible for Pradaxa?

A. He has some oversight responsibility.

HARVEY

Q. And do you have any evidence that he has ever even raised the question with his colleagues of whether the Pradaxa label should direct doctors to test and target a range of 50 to 150?

MR. MOSKOW: Objection to form.

A. Based upon his slide presentation, he infers that there's discussion ongoing.

Q. Right. And --

A. But I don't have -- I have no direct knowledge of what the FDA's discussing this minute.

Q. How long ago was the first of those slide presentations you referenced?

A. December 2014.

Q. And can you point me to --

A. The second one was December 2015.

Q. Can you point me to any action the FDA has taken to make modifications to the label along the lines of a plasma concentration recommendation since December 2014?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. None as of this morning.

HARVEY

MR. SCHMIDT: Why don't we break for lunch.

THE VIDEOGRAPHER: Off the record at 1:20.

(Recess taken.)

THE VIDEOGRAPHER: Here begins media number 4 in the video recorded deposition of Dr. Brian Harvey. We're back on the record at 2:30.

BY MR. SCHMIDT:

Q. Doctor, you've been critical of Boehringer for not doing more to evaluate and warn about plasma concentration. True?

A. Yes.

Q. And your testimony as I understand it is that a reasonable company would do more to evaluate and warn about plasma concentration; correct?

A. Yes.

Q. Now, I think we've talked about this. You know this question has been raised about plasma monitoring, including by Dr. Temple, with respect to all novel oral anticoagulants; correct?

HARVEY

A. Yes.

Q. And there are five other companies other than Boehringer involved in making novel oral anticoagulants. You understand that; right?

A. I know there are others. I don't know the exact number, but --

Q. There's Pfizer and BMS on Eliquis, there's J&J and Bayer on Xarelto, and there is Daiichi on Savaysa. Did I get the name wrong?

MS. PRESBY: Is there a question?

THE WITNESS: Is there a question?

Q. Are you aware that --

A. I'm aware of -- that there are many, many folks in the field.

Q. Are you aware of those five companies specifically?

A. I have read about them. I haven't studied them for my report.

Q. As best you know, are those all reasonable companies?

MR. MOSKOW: Objection to form.

A. My report was confined to BI and what they did. I didn't -- as part of the scope, I

HARVEY

didn't look at the whole pharmaceutical industry nor the competitive product.

Q. You've worked with some of those companies and at some of those companies; right?

A. Yes.

Q. In your experience are they reasonable pharmaceutical companies?

A. I would say, having worked at Pfizer, Pfizer is a reasonable pharmaceutical company.

Q. Is BMS?

A. I didn't work directly with BMS.

Q. From your experience.

A. I haven't had a direct experience working with them. I would like to in the future but I have not.

Q. You're currently in negotiations to work with them?

A. That's true.

Q. Is J&J a reasonable company?

A. Yes, it is.

Q. Is Daiichi a reasonable company?

A. I haven't had a lot of direct experience so I wouldn't be able to say.

HARVEY

Q. You mentioned Bayer. Is Bayer a reasonable company?

A. I haven't worked directly with them either so --

Q. I thought you said you had in the past?

A. Only when I was at FDA because they were a maker of Naproxen and they were part of the nonsteroidal issue. So it was very, very indirect.

Q. Have any of these other companies taken any steps regarding plasma concentration, whether it's gathering data, analyzing data, sharing data, that you can point me to?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. Yeah, I -- the focus of my report was on BI and what BI did and did not do, not on the competitors.

Q. Let me ask my question again. Can you point me to any steps that you know of, in your review here or more broadly, that any of these companies have taken to collect plasma concentration data, analyze it, or report it to

HARVEY

the public or the FDA that Boehringer has not taken?

MR. MOSKOW: Objection to form, asked and answered.

A. As I said, and we talked about how my report was 120 pages and it took 200 hours, that was focused on the task at hand, and doing a survey on the entire competitive landscape wasn't in the scope of my report, and I didn't pursue that information. If I had known that that would have been important to do, I would have done so. It wasn't part of the scope of my report.

Q. You're talking about what reasonable companies would do; right?

A. Yes.

Q. Here we have reasonable companies working in the very same -- with the very same types of medicines; right?

MS. PRESBY: Objection.

A. Yes.

Q. So can you point me -- I get your qualifier, I get your explanation. My question is simple: Can you point me to any steps that

HARVEY

these other companies have taken that BI hasn't taken?

MR. MOSKOW: Objection to form.

A. No, I can't.

Q. Can you point me to any company that has taken the steps that BI has taken in terms of collecting plasma data, analyzing it, sharing it with regulators and publishing on it?

A. I haven't -- I haven't researched that.

Q. Okay. Can you point me to any company that's done that?

MS. PRESBY: Same objection.

MR. MOSKOW: Objection, asked and answered.

A. It's not -- wasn't in the scope of my research.

Q. I can ask you questions that I think are relevant that you didn't take the time to do, so --

A. And so therefore --

Q. Please let me finish.

A. -- I don't have information --

HARVEY

Q. Please let me finish.

A. You just asked me the question and I'm answering it.

Q. Please let me finish. We're not arguing. Please let me finish. I'm allowed to ask you questions about research I think is relevant given the opinions you're offering that you haven't done.

So my question is in all of your research have you seen any efforts that any other companies have taken, similar to what BI has done, in terms of gathering plasma data, analyzing plasma data, reporting it to regulators, and publishing on it?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. So I have not researched other companies and therefore I can't cite what other companies have done.

Q. Okay. Would you agree with me that you would not want a dose adjusted in a way that hurts patient safety?

MR. MOSKOW: Objection to form.

A. I agree.

HARVEY

Q. Would you agree with me that if you don't -- if you dose-adjust and you're not careful in how you dose-adjust, you could hurt patient safety?

MR. MOSKOW: Objection to form.

A. Yes, I agree.

Q. For example, we have talked about blood testing. Are you aware that it matters, in terms of getting a reliable blood test, when you test the patient relevant to when they last used the medicine?

A. Can you clarify that? I don't remember talking about when to test. So can you rephrase the question or reask the question?

Q. Yeah. And I didn't ask you about -- I didn't say we talked about when to test. We talked about blood testing.

A. Okay. We talked about blood testing. Yes, I remember.

Q. Are you aware that if you're doing a blood test you need to be careful to do the test at the right point in time relevant to when the patient last took the medicine?

HARVEY

A. Yes, I do.

Q. And what is that point in time?

A. The thought is that you want to make sure that you catch the patient at a steady state, because if you're getting them as the curve is going up or going down, you want to make sure they're at the trough of the steady state because that's a more reproducible time point and more representative of what their concentration is.

Q. So when should you be trying to test patients relevant to when they last took the medicine?

A. Well, it depends. You know, that would be something that an expert pharmacologist would calculate based upon when steady state was reached, five half-lives. There's a whole paradigm that one would follow and I would defer to a pharmacologist on that.

Q. Do you know when they should be tested relevant to when they last took the medicine?

MS. PRESBY: Objection.

MR. MOSKOW: Objection to form.

HARVEY

A. So like I said, as a regulatory person I would say it needs to be determined by the appropriate pharmacology, you know, the PK person. And my understanding is, you know, you've got to catch it at steady state at the trough.

Q. Okay. You're not that pharmacologist PK person; right?

A. That's correct.

Q. So you don't have a specific opinion as to what the right time to test is after their last dose?

MR. MOSKOW: Objection to form.

Q. Correct?

A. That's correct.

Q. And -- but you do understand it generally to be at trough, whatever that is?

A. Yes.

Q. And so the numbers we were talking about earlier, the 50 to 250 or a narrower range, those are trough concentrations?

A. The 50 to 150, those are trough --

Q. And then if you test at the wrong time, that can have safety consequences; right?

HARVEY

A. Can you rephrase that, because there are -- you may not get an accurate reflection of steady state, but if it is extremely low or extremely high, it's still informative but not as reproducible.

Q. Let me ask you that question then. If you test at the wrong point in time, can you get an inaccurate reading, or misleading reading -- however you want to characterize it -- that leads you to make a dose adjustment that you would not make if you tested at the right point in time?

MR. MOSKOW: Objection to form.

A. Yes.

Q. And could that have safety consequences?

A. Yes, it could.

Q. And it could in either direction; right? Exposing to too much bleed or exposing to too much stroke?

A. Yes, it could.

Q. Now, are you also aware of whether there is data that even in a controlled setting, when scientists take care to make sure

HARVEY

that they do test at the right point in time, that initial test results that potentially suggest someone might have an outlier plasma concentration if you retest in a couple of months, that doesn't prove to be the case when you retest? Are you aware of data showing that?

MR. MOSKOW: Objection to form.

A. Can you rephrase or can you reask the question?

Q. Sure. Your testimony from before lunch is that you should do a single test, sometime I guess around the time someone starts using the medicine; right?

A. Yes.

MS. PRESBY: Objection.

Q. And are you aware of data showing that a single test does not always prove accurate over time?

A. I -- in some of the articles there is that discussion, yes.

Q. And the concern is that if you dose-adjust based on a single test, that might lead to a dose that actually is not the best

HARVEY

dose over time; right?

MR. MOSKOW: Objection to form.

A. That's correct. If you only did a single test, that's correct.

MR. SCHMIDT: And just let me show you one of those studies. Can I get the Chan study? Are you familiar with the Chan study from 2015? Was it cited? Is it on the reliance list?

(Harvey Exhibit No. 11 was marked for identification.)

BY MR. SCHMIDT:

Q. I've given you Exhibit 11, a 2015 article, the lead author is N.C. Chan. Have you seen this before, Doctor?

A. I've seen an article that's real-world variability with Eikelboom as an author. Sometimes when you're looking at it on a screen it looks a little different, but there's a lot in here that looks familiar.

Q. Let me show you a couple things about this. First of all, if we look at the first page of the article, do you see that there's a summary?

HARVEY

A. Uh-huh.

Q. And if you look right before the conclusions in the summary -- let me just ask you. To be fair to you, why don't you go ahead and read that summary to yourself.

A. Okay. I've read it.

Q. This is a study, as I understand it, that involved testing the blood levels of patients taking Pradaxa at what they called baseline, which is shortly after they started using the medicine, and then every two months after; right?

A. Uh-huh.

Q. Yes?

A. Yes.

Q. And what they were trying to see is if at that first baseline test they had either a very high or a very low blood concentration, if you did nothing at all, would that persist across the later tests; right?

A. Correct.

Q. And what they found, in the second-to-last sentence of the introduction, is that up to 40 percent of patients whose trough

HARVEY

levels were in the upper extremes and up to 80 percent of patients whose trough levels were in the lower extremes at baseline showed subsequent levels that fell in the middle quartiles.

Do you see that?

A. Yes, I do.

Q. So the idea there is they're saying a large number of patients in their review who initially looked like they have high or low levels end up in the middle of the range with later tests; correct?

MR. MOSKOW: Objection to form.

A. That's what they state, yes.

Q. If you look at the conclusion they reached from that -- look with me if you would at 359 -- they say: "Our data do not support the concept that a single Hemoclot measurement" -- that's a way of testing blood concentration; right?

A. Right.

Q. And one you endorse; right?

A. Yes, one of the ways.

Q. "Our data do not support the concept

HARVEY

that a single Hemoclot measurement can be used to identify patients with consistently high or low values."

Do you see that conclusion?

A. Yes, I do.

Q. Do you agree with that conclusion?

A. Based upon the data they present, I think that's a valid conclusion with the way the study's designed.

Q. Have you seen any contrary data on this point of how predictive is the initial blood test of later blood tests?

A. No, I haven't.

Q. Let me show you one other article. Another -- are you aware of study data looking at whether -- strike that.

In the U.S. and around the world there are different doses available for Pradaxa; right?

A. Yes.

Q. In the U.S. there are now three doses available, 75, 110, and 150, and they vary when you're supposed to use those doses; correct?

MR. MOSKOW: Objection to form.

HARVEY

A. Yes.

Q. And, for example, for most patients who have atrial fibrillation, the 150 is recommended?

A. Based upon the current U.S. label, yes.

Q. That's been true throughout the life of the medicine in the U.S.?

A. Yes.

Q. For patients who have renal impairment, the 75 is recommended?

MR. MOSKOW: Objection to form.

A. Yes.

Q. And for patients for some new indications other than stroke prevention, the 110 has been approved?

A. That is correct.

Q. So doctors have different dosing options and they can vary them even more because every one of those doses is intended to be twice a day; right?

A. Yes.

Q. When a doctor varies from the dosing recommendations, that's referred to as

HARVEY

off-label dosing; right?

A. Yes.

Q. And, for example, if we're talking about your stroke prevention patient who doesn't have the designated renal impairment in the label, they should be using, according to the label, according to the FDA-approved label, 150 milligrams twice a day; right?

A. Can you rephrase that?

Q. Sure. According to the U.S. label that's been approved by the FDA, the recommended dose for patients who are taking Pradaxa for stroke prevention and do not have the renal impairment designated in the label is 150 milligrams twice a day?

A. That's correct.

MR. MOSKOW: Objection to form. Please wait to get the objection on.

THE WITNESS: I'm sorry.

Q. So if a doctor prescribes 110 or 150 three times a day, those are off-label doses; right?

A. That's correct.

Q. And a doctor can -- a doctor has the

HARVEY

ability to do that under our system; right? They can prescribe off-label whether it's doses or actual uses of the medicine; right?

A. That's correct.

Q. And -- strike that.

So an off-label dose of Pradaxa could be either a higher dose or an under-dose; correct?

MR. MOSKOW: Objection to form.

A. Can you ask the question again with the context?

Q. Sure. If a doctor -- a doctor can prescribe Pradaxa in an off-label dose either by prescribing a higher dose than recommended or a lower dose than recommended; correct?

A. That's true, yes. Correct.

Q. Are you aware of study data that evaluates safety outcomes when doctors prescribe Pradaxa or other NOACs at an off-label higher dose or an off-label lower dose?

A. I've seen some literature where that's done.

Q. Do you recall what that literature

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shows?

A. I remember a paper by Graham in the Medicare population where a larger number of patients were prescribed 75 milligrams more than what one would have thought from the U.S. label, and they showed a lower rate of significant bleeds.

Q. Do you know those 75-milligram patients in the Graham study were specifically off-label?

A. Well, the way the article described it is that based upon the U.S. label, they should have received 150 but they received 75. So by your definition, that would be off-label.

Q. Okay. Are you aware of any other publications looking at that?

A. There have been -- there was a publication coming out of Canada where they looked at 150 and 110, because in Canada, 110 would not be off-label, but that would be considered off-label in the U.S.

(Harvey Exhibit No. 13 was marked for identification.)

BY MR. SCHMIDT:

HARVEY

Q. Let's look at the Graham article that I believe you just referenced. Is that what I've marked as Exhibit 13?

A. Uh-huh, yes.

Q. Can you point me to that language you were referencing where he suggests to you that there was a lot of 75-milligram off-label use?

A. Well, not using that, the term "off-label," as we discussed. Let's see.

Okay. So on page 162, the second column, in the top paragraph, the first sentence is just leading in. The second sentence -- let's see. Third sentence: "Although we lack the laboratory data on creatinine clearance and are uncertain of the accuracy of kidney disease coding, our results suggest that many patients treated with this lower dose" -- I'm assuming they mean the 75 -- "on the basis of the current product label, they should have been treated with a 150-milligram dose. In this setting of moderate, mild or no renal impairment, off-label use of the 75-milligram may result in patients being under-dosed and could explain

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why we found no difference in the risk of ischemic stroke, major gastrointestinal bleeding, or mortality between warfarin, the lower dose, and" -- let's see. "On the other hand, if most of the patients treated with the 75-milligram dose actually had severe renal impairment, this would suggest that the dabigatran dosing based on pharmacological modeling was suboptimal."

So there they discuss variations of prescribing from the U.S. label.

Q. Okay. So that helps. I see now what you're referencing. Let me see if I understand it. This is this Graham FDA publication we've talked about a couple of times today; right?

A. Yes.

MR. MOSKOW: Objection, form.

A. I believe so.

Q. This is an FDA publication; right?

MR. MOSKOW: Objection, form.

A. Yeah, let me just -- because the authors are from FDA. Let me just see if they have the disclaimer.

Q. They do have the disclaimer. This is

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a study authored by FDA employees; correct?
A. Correct.
Q. And funded by the FDA; correct? If you look at source of funding on 163.
A. Yes.
Q. And in this article, the language you just pointed me to, they make the point that they can't be sure but it looks to them like some of the 75-milligram patients should have been using 150; correct?
A. That's correct.
Q. And they should have been using 150 based on the label; right?
A. The U.S. label, yes.
Q. And then they say this raises the question of whether patients treated off-label with a 75-milligram dose would have experienced improved outcomes for ischemic stroke and mortality had they been treated with the 150 dose instead.
Do you see that?
A. Yes.
Q. So they're raising the question there might be off-label use of the 75-milligram and

HARVEY

that might be bad in patient outcomes; right? Might lead to more death and more ischemic strokes; correct?
A. In that paragraph.
Q. Yes.
A. Then they go on.
Q. Then in the table below, they give the data supporting what they saw with 75-milligram patients and what they saw with 150-milligram patients; right?
A. Correct.
Q. And this definitionally is second generation data; right? This is second generation Pradaxa they're looking at; correct?
A. That is my understanding, yes.
Q. A real-world United States study involving elderly patients; correct?
A. Yes.
Q. And what they find is in table 4 when they compare -- they compare the 75-milligram dose and the 150-milligram dose to warfarin on a number of important measurements; right?
MR. MOSKOW: Objection to form.
A. Which table?

HARVEY

Q. Table 4.
A. Yes.
Q. And what they find is that on ischemic stroke, the 75-milligram dose is not statistically different from warfarin, but the 150-milligram dose is statistically better than warfarin; correct?
A. Correct.
MR. MOSKOW: Objection to form.
Q. For major gastrointestinal bleeding, they find that the 75-milligram dose is not statistically different from warfarin but that the 150-milligram dose is statistically higher; correct?
MR. MOSKOW: Objection to form.
A. Yes.
Q. For intracranial hemorrhage they find that both the 75 and the 150 are statistically lower than warfarin?
MR. MOSKOW: Objection to form.
A. Yes.
Q. And for mortality -- which is death; right?
A. Yes.

HARVEY

Q. They find that mortality is not statistically different between warfarin and the 75-milligram; correct?
MR. MOSKOW: Objection to form.
A. Yes.
Q. But they find that deaths are statistically significantly lower with the 150 than they are with warfarin; correct?
A. Yes.
Q. By 24 percent?
A. Yes.
Q. Now, in terms of those end points, in terms of those metrics, ischemic stroke, major gastrointestinal bleed, intracranial hemorrhage, mortality, would you agree with me that on average death is worse than a major gastrointestinal bleed?
A. Are you saying a nonfatal -- since upwards of 10 percent of gastrointestinal bleeds lead to death.
Q. Okay. 10 percent death versus 100 percent death, which is worse?
A. 100 percent death obviously.
Q. So you would take the mortality

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finding as a more important safety finding than the major gastrointestinal bleed finding?

A. I would analyze both and put them in context and agree with you that mortality is important to consider, as mortality could include all cause mortality, which means all the various categories.

Q. When you're assessing the safety of a medicine and the efficacy of a medicine, is the mortality rate more important to you than the major GI bleed rate, or do you weigh them equally?

A. I would put the highest priority on mortality, but I wouldn't ignore the other indications, since intracranial bleeds that don't kill patients can still have major debilitating and a major impact on the rest of their lives.

Q. You just got to the one I was going to ask you. Intracranial bleeds can be incredibly serious; right?

A. Yes.

Q. And they're viewed as of great, great concern to treaters.

HARVEY

A. Yes, very much so.

Q. Would you put more weight on avoiding intracranial hemorrhages than you do on avoiding major gastrointestinal hemorrhages?

A. Can you rephrase that?

Q. Sure.

A. Since it's sort of an oversimplification the way you've asked it.

Q. Every drug involves tradeoffs; right?

A. Correct.

Q. Here on this table we see some of the tradeoffs. Pradaxa according to this table is better than warfarin on ischemic stroke, better on intracranial hemorrhage, better on death, worse on major GI bleeds; right?

A. Right.

MR. MOSKOW: Objection to form.

Q. So my question is if you have a choice between having a drug that's better on intracranial hemorrhage versus one that's better on major GI bleeds, how do you weight those two?

A. Well, I think -- I don't think that I can give you a good answer, and that has been

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something that's been debated within FDA on how you compare different types of events.

MR. SCHMIDT: Let me show you an article published by Hart.

(Harvey Exhibit No. 14 was marked for identification.)

BY MR. SCHMIDT:

Q. Entitled "Intracranial Hemorrhage in Atrial Fibrillation Patients During Anticoagulation with Warfarin or Dabigatran."

A. Published in the Stroke Journal.

Q. A reputable journal; right?

A. Yeah, but not published in the gastrointestinal literature.

Q. I don't want to get into any professional turf wars.

MR. MOSKOW: I think you already got it.

Q. My question is simply do you know if you've seen this article before?

A. Yes, I have.

Q. Look with me if you would at the very first sentence of this article. I'll read it out loud. "Intracranial hemorrhage is the most

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feared complication of warfarin anticoagulation in older patients with atrial fibrillation and is responsible for the bulk of disability and death from anticoagulation-associated bleeding."

Did I read that correctly?

A. Yes, you did.

Q. Do you agree with that?

A. I would need to see the data. More patients used to die from GI bleeds, and now with the advent of proton pump inhibitors, the number of deaths from GI bleeds has gone down, and yet interventions for intracranial hemorrhage have not improved much over that same time period. So this statement on its face could be true.

Q. You're not sure?

A. I would have to see some of the current data since an elderly person who had a significant GI bleed then could have hypotension, go into renal failure, and have, you know, many debilitating residual effects that parallel what could happen -- you know, not the same but as debilitating but in a

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different way than in an intracranial bleed.

Q. I think we can both agree a GI bleed can be quite serious; right?

A. Leading to death in cases.

Q. It could be not serious; right?

A. That's true.

Q. My question is just do you know if this is a true statement that generally speaking intracranial hemorrhage is the most feared complication of warfarin?

A. I think in general, and especially in the stroke community, that's true.

Q. Look with me if you would at page 6 of this article, please. If you look at the first full paragraph, it provides some data supporting that proposition we were looking at. "Intracerebral hemorrhage is the most devastating complication of anticoagulation, with mortality rates exceeding 50 percent in most studies."

Did I read that correctly?

A. Yes, you did.

Q. Do you have that general understanding, that over half of people who

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have intracranial hemorrhages die from it?

A. I think that the understanding of the -- of the pathophysiology of the hemorrhage has evolved given our better ability to image it with MRI and advanced CT. And I think with that refined testing we are better able, you as a -- the clinical community is better able to diagnose it. And so the references -- reference 1 is actually from 2007, which was a while ago. Some of the other references are older as well.

I think the point that they're making is that it's a serious complication, and I certainly wouldn't disagree with it. I would only have problems with some of the numbers. But 50 percent mortality is well above the 10 percent mortality we just talked about with GI bleeds.

Q. And that's where I was going next. If you had the choice of making the tradeoff, something that was better on GI bleeds but worse on intracranial hemorrhage, versus something that was worse on intracranial hemorrhage but better -- I guess they're the

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same thing twice. Let me start my question again.

MR. MOSKOW: I actually liked that question. Let's just stick with that one.

MR. SCHMIDT: That's why I do the hand thing, to keep myself straight.

Q. Doctor, if you had the choice between a medicine that was better on GI bleeds but worse on intracranial hemorrhage, versus a medicine that was worse on intracranial hemorrhage but better on GI bleeds, how would you choose between those two, all other things being equal?

A. Well, if I was looking at this from a regulatory perspective, then --

Q. You know what? I got to withdraw it. I goofed on my question again. I'm so sorry. Let me try it one more time.

If you had something that was better -- if you had a medication that was better on GI bleeds, worse on intracranial hemorrhage, versus one that was worse on GI bleeds, better on intracranial hemorrhages, how

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would you pick between those two, all other things being equal?

A. So as a regulator, I would tend to favor those that are better on intracranial hemorrhage. As a clinician, or if I was treating an individual, it would be based upon the characteristics of that individual, their past history, if they had a history of GI bleeding. So I would try to tailor the treatment to the individual and their, you know, desires as well. Different individuals have different risk tolerances and some fear certain things as well, and that's part of the doctor-patient relationship.

Q. Let's go back to Exhibit 13, the Graham article, and let's just close that out. Do you understand from the language we were looking at about the 75-milligram dose that the Graham authors are at least raising the question of -- are raising the suggestion that their data might indicate that under-dosing Pradaxa patients is undesirable in terms of safety outcomes?

A. I don't interpret it that way. I

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think they have said that they see a decrease in efficacy with a 75-milligram dose, but they also see a corresponding decrease in bleeds with the 75-milligram dose, since in the summary at the very end of the paper the 75-milligram dose was associated only with a reduced risk of intracranial hemorrhage.

Q. Versus warfarin?

A. So they were -- they were citing that there was a differential effect.

Q. Let me be specific.

Do you remember that language we looked at where they say this raises the question of -- it's on page 162. "This raises the question of whether patients treated off-label with a 75-milligram dose would have experienced improved outcomes for stroke and mortality had they been treated with 150-milligram dose instead"?

A. Yes.

Q. And they're suggesting there that under-dosing might not be a good thing, you might get better results on stroke and better results on mortality with the proper dosing;

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correct?

A. Yes, that's correct.

Q. And this article -- then we can put it aside -- if we look at page 160 under the discussion.

MR. MOSKOW: 160?

MR. SCHMIDT: 160, yes.

Q. The second sentence under the discussion says: "The level of risks were similar in direction and magnitude to those observed in the randomized trial, RE-LY, in which dabigatran 150 twice daily was compared with adjusted dose warfarin therapy."

Did I read that correctly?

A. Yes, you did.

Q. That's the idea we talked about earlier in the day that these authors looked at their real-world data results and said these are consistent with what we saw in RE-LY; correct?

MR. MOSKOW: Objection to form.

A. Yes.

MR. SCHMIDT: Let's go back to -- I was asking you about whether you had

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seen other data on real-world implications of over- or under-dosing.

I want to show you an article that I've marked as Exhibit 12. The lead author is Steinberg.

(Harvey Exhibit No. 12 was marked for identification.)

BY MR. SCHMIDT:

Q. I will represent to you that this is not on your list of articles. Does that mean you have not reviewed this article before?

A. I have not reviewed this specific article.

Q. Let's look at what this article did. If you look with me at page -- let's look at the first page.

Do you see the objectives?

A. Yes.

Q. "This study assessed the frequency of off-label NOAC doses among atrial fibrillation patients and the associations between off-label dose therapy and clinical outcomes in community practice."

Do you see that?

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A. Yes, I do.

Q. So what they were doing is they were looking at whether patients who received a dose other than recommended in the label, whether that impacted safety outcomes; correct?

A. Correct.

Q. And if you look, they report their data in various tables and charts, including, for example, table -- the table on page 2602. The easier way to do it is let's look at the results on the first page.

Do you see in the results they report that about 9 percent of their patients were under-dosed, 3.4 were overdosed, and 87 percent were dosed according to the label?

A. I'm sorry. What page again?

Q. Go back to the front page. If you look at the first sentence under Results, do you see that they report just over 9 percent of their patients were under-dosed, just over 3 percent were overdosed, and the rest, 87 percent, received the recommended dose?

A. Yes, I see that, yeah.

Q. And they found that patients who

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were -- received off-label doses were more likely to be older, and that was true both for under-dosing and overdosing. They were both about 10 years older than the on-label dosed people?

A. Yes, I see that.

Q. Their conclusion is that overdosing -- if you look at the conclusions on the first page, overdosing and under-dosing are associated with increased risk for adverse events.

Do you see that?

A. Yes, I do.

Q. And they provide data supporting that proposition; right?

A. Yes, they do.

Q. They make a similar conclusion on the last page of the article, 2604. They say: "Most patients treated with NOACs for stroke prevention receive doses according to FDA-approved labeling; however, a significant minority did not receive such doses, and off-label doses were associated with increased risk for adverse events."

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Do you see that?

A. Yes, I do.

Q. "Careful attention to recommended doses and additional studies of these agents in patients underrepresented in clinical trials may improve clinical outcomes." Correct?

A. Yes.

Q. So these authors were purporting to say that if you vary from the recommended dosing, you can have an increase in safety events; correct?

A. Yes.

MR. MOSKOW: Objection to form.

Q. Have you seen any contrary data?

A. Well, actually, I see something within their own paper that's a confounding variable. They also mention in the results section, where you did not read, was that the off-label -- in addition to the off-label individuals being older, they also were more likely to be female and they were more likely to not be treated by super-specialists, you know, electrophysiologists. And so you have the variable that the individuals that were

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off-label were also more likely to be female, and that can increase the risk. And higher level of care or more specialized care would lead to a lower risk, and they were less likely.

So both of those would actually contribute to the results as well, and they don't mention that in their conclusion.

Q. Move to strike as nonresponsive. Have you ever -- have you seen any contrary studies that indicate that off-label dosing of patients does not lead to adverse outcomes?

A. And let me say that data is here in this paper where that part was left out.

Q. Well, you're making a different point. You're saying that they might be over-extrapolating from their findings because of a confounder; correct?

A. Correct.

Q. My question is different. My question is -- first of all, have you done any analysis of whether there is, in fact, a confounder in this paper or the effect of the confounder, how much of the effect it might

HARVEY

wipe away?

MR. MOSKOW: Objection to form.

Q. Have you done that?

A. I've done it in my head since you highlighted that the difference in age between 79 and 70 was significant, and yet, then when you go down below, there's a similar difference on more likely to be female, and so --

Q. So what's the impact of the female difference that you've been able to calculate in your head?

A. I think a portion of the increased risk of the off-label use is due to the imbalance of females.

Q. What portion?

A. Can't say.

Q. Okay. So let's come back to my question which is have you seen any data contrary to the conclusion these authors reach from their data, i.e., data that is data showing that off-label doses are not associated with higher safety problems? Have you seen any contrary data?

A. I'm trying to remember the

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Canadian -- the Canadian paper. I can't give specific examples, so no.

Q. Would you want to be sure, before you implemented a testing and dose adjustment scheme like the one we talked about before lunch, that it would actually lead to safer results and not lead to patient harm?

A. I would agree that that scheme should be tested by the sponsor, the data generated and that evaluated -- and submitted to the FDA in an sNDA for them to do a formal review, I agree.

Q. Has such a test been done to validate that kind of testing and dose adjustment regimen?

A. I don't know of any study done by the sponsor to formally test it, and I don't know of it being submitted to FDA for their review.

Q. Now, you've talked about -- you talked about this morning how you have been involved in designing studies; right?

A. That's correct.

Q. Have you sat down and tried to design what a study like the one you just described

HARVEY

would look like in terms of how it would be conducted and the patient population size you would need?

A. No, I have not.

Q. There are limits to what can feasibly be conducted in terms of study size; correct?

MR. MOSKOW: Objection to form.

A. I'm not sure what criteria one would use since the study size is really dictated by the treatment effect and the incidence in which events occur.

Q. Right. I guess that's where I'm getting. Have you modeled out, if you were to try to do a study designed to look at whether the testing and dose adjustment regimen you talked about before lunch, whether a study to evaluate the safety of that would require 100 people, 1,000 people, 10,000 people, 20, 30,000 people?

A. Well, we know the original -- so the answer is no. And we know the original RE-LY trial was what, 18,000 patients? So --

Q. This would be a different study?

A. This would be a different study.

HARVEY

Q. So you can't just say because RE-LY was 18,000, that would be enough for this; right?

A. That's correct.

Q. Let me show you one more thing. Have you written down what you think the label should say? Let me ask more broadly.

A. I haven't written down --

MR. MOSKOW: Wait for the question.

A. Okay.

Q. Why don't you finish your answer, sir.

A. I haven't written down --

MS. PRESBY: There's no question.

A. -- anything other than what I've written in my report.

Q. Have you written what you think the Pradaxa label should have said at launch or should have said at any point after?

A. No.

Q. Have you tested that label with real-world doctors to see if they understand what you're trying to communicate and if they think it makes sense?

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MR. MOSKOW: Objection to form.

Other than himself.

A. If I didn't write the label, how could I test it with real-world doctors?

Q. You haven't?

A. I'm confused. So can you rephrase.

Q. Sure. Have you consulted with any doctors who prescribe anticoagulants about your concerns about the label to get their reaction to them?

A. No, I didn't.

Q. Have you tried out proposed labeling language with them to see if in their view it would be more informative to them than what Boehringer gives them?

MR. MOSKOW: Objection to form.

A. No. And can I ask the question, I didn't think I was supposed to be reaching out to others outside of the process. So I haven't talked with anybody outside of counsel.

Q. Have you talked with any -- have you tested your -- have you tested specific warnings with regulators in any way to see if it would be acceptable to regulators or if they

HARVEY

would agree with your opinion that there are better ways to warn than what they have approved?

A. No.

MR. MOSKOW: Objection to form. Specifically with regard to Pradaxa?

MR. SCHMIDT: Yes.

A. No, I have not.

MR. SCHMIDT: Let me give you what I'm going to mark as Exhibit 15.

(Harvey Exhibit No. 15 was marked for identification.)

BY MR. SCHMIDT:

Q. You will see this is an exhibit from another deposition from Dr. Baruch. And let me just ask you, if you'll look at this I will represent to you that this is labeling language he wrote regarding monitoring. I'll just ask you to read it to yourself, then I'll ask you a question about it.

A. Okay.

Q. Is this -- can you endorse this in your view as an appropriate way of warning doctors about how they should warn patients

HARVEY

about the need to test blood levels and dose-adjust?

A. Well, there are many elements of this I like, especially the rechecking the level before changing the dose, which addresses some of the concerns that have been raised. The level greater than 180, I think that can be debated, but it's -- that's close enough -- I mean that's -- I might say 150, but the overall structure I agree with. And I think there's agreement on the 50. Once again, rechecking, and then if it's less, then going to warfarin or another product. And then the drug levels being measured at LabCorp's request or whatever's using mass spec is certainly a good way to measure drug levels and available in the U.S.

Q. Let me break that down a little bit. Have you seen this before today?

A. No, I have not.

Q. When you told me your opinion on how blood levels should be checked, you didn't say anything about rechecking a couple weeks later; correct?

HARVEY

A. No, I didn't.

Q. Are you now changing that opinion to say in fact you should recheck a couple weeks later?

MR. MOSKOW: Objection to form. You can answer.

A. Nothing that I said in my general outline negated rechecking. I was giving a broad overview. This is a more detailed plan. And I think the idea of rechecking makes a lot of sense. I hadn't gone into that detail. And as I said with many of the things, I would have deferred to others who are experts in the specific area about testing and treating since I'm not here as a medical expert.

Q. So how often should there be rechecking?

A. Well, if you can rephrase since we had similar conversations. The idea is that as a regulatory expert I have a general idea, and then the specifics are, you know, filled in by the experts in those areas.

Q. Well --

A. I would like it to be a data-driven

HARVEY

process, so I think having the experts in those specific areas looking at the data on what makes sense of how often to check, and I think in my Exhibit 10 we went over some of those issues where I was saying -- it didn't get written down -- that if someone has renal function issues, there needs to be some periodic checking because renal function can change over time. And if you look at FDA labels, they often are not prescriptive on how often to check things. They give more generalized guidelines to allow for the practitioner to give the specifics.

Q. I'm asking you about your labeling opinions. What should doctors be told about whether and how often they should recheck after an initial blood test?

A. And I'm saying I agree with this general framework and I have no specific opinions on how often the testing should be done.

Q. Do you have any specific opinions -- you have no specific opinions on how often testing should be done; correct?

HARVEY

A. That's correct.
Q. Do you have any opinions on --
A. After the initial test, yes.
Q. Right. Do you have any opinions on whether there should be a mandatory second test after the initial test?
A. Once again, FDA rarely ever has mandatory testing. That's not how they regulate. They give guidelines and suggestions and labeling advice for the practitioner to then consider as they're treating their individual patient.
Q. Do you have any recommendation regarding subsequent testing?
A. My general recommendations are -- is that should there be changes in the patient so if they have been on -- if they're on the Pradaxa for a long period of time as they are advancing in years, it would be prudent to do an additional test then. If during routine blood work there was a worsening of the patient's serum creatinine, you know, that would warrant some consideration and additional testing. If the patient changed medications,

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certainly if they had a GI bleed or had GI symptoms and a positive stool hemoccult test, you know, all of these things should be taken into consideration. It's not a blanket test once and you're done, just like I don't believe in no monitoring, you know, in that paradigm.
Q. Would you recommend subsequent tests as a matter of course, absent some kind of special circumstance like you were just listing?
MR. MOSKOW: Objection to form.
A. It would have to be based upon the data that was developed. The sponsor needs to generate data and make a proposal to FDA and submit it in an sNDA, and they need to evaluate it to have that inform the label. In the regulatory sense, having a plan in the absence of data is not -- is not the best way to do it.
Q. You understand that BI has generated data on plasma concentration; correct?
A. Yes, I do.
Q. And they have submitted their opinion on that data to the FDA, which is that it does not require routine monitoring or blood

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checking; correct?
MR. MOSKOW: Objection to form.
A. So my understanding is that --
Q. Is what I said correct?
A. Can you clarify how it was submitted?
Q. Sure. Do you have an understanding that Boehringer has communicated to the FDA its view that based on its data, blood tests for plasma concentration on any form of routine basis are not required?
A. And my clarification --
Q. Do you understand that?
A. I -- I don't understand your question because I don't know if that was in a phone call or to the IND or to the annual report.
Q. In any way. Have they communicated in any way? How about in the label?
A. But that's what I'm saying, is that it should be communicated in an sNDA, so for FDA to evaluate that data and have them decide whether or not monitoring --
Q. Do you understand -- you understand that Boehringer's view is that routine monitoring and routine blood tests are not

HARVEY

required?
A. I understand that that was their -- the paradigm that they followed before they had -- even had the RE-LY data.
Q. That's their view up until this day, having analyzed the data; correct?
A. That's currently their view as well.
Q. And they have communicated that view to the FDA. They haven't kept that view hidden from the FDA; correct?
A. That's correct.
Q. So they have shared their view. You disagree with that view; right?
A. Could you clarify? Because I thought we were talking about them submitting the data to FDA.
Q. Do you disagree with Boehringer's view?
A. I disagree with Boehringer's view.
Q. So what is your view as to what doctors should be told about whether and when they need to do a blood test after the first blood test?
MR. MOSKOW: Objection to form.

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A. I believe that the sponsor, BI, needs to study this in a systematic way because the Graham article was not a randomized controlled clinical trial. The methodology was something less than a randomized controlled trial. So in a randomized controlled trial, these ideas need to be tested, and that information, that data that's generated needs to be submitted to FDA in an sNDA for the labeling change.

Q. Move to --

A. And --

Q. Move to strike as entirely nonresponsive. Doctor, I understand you think Boehringer should do further studies; correct?

A. Correct.

Q. Okay. But you haven't specified how those studies should be designed; correct?

A. I have in giving specific suggestions on areas that need to be addressed.

Q. Have you identified a specifically feasible way of doing the study you believe BI should do?

A. I have not taken it to that extreme yet.

HARVEY

Q. That extreme being feasibility?

MR. MOSKOW: Objection to form.

Q. Correct?

A. Feasibility is in the eye of the beholder as we saw with pediatric studies and modeling.

Q. So here's my question. Do you have a further opinion, beyond opining that they should do a study, do you have a further opinion that based on the current data as it exists, doctors should be told to do blood tests on their patients with Pradaxa?

MR. MOSKOW: Objection to form.

Q. Do you have a current opinion based on the current data? Yes or no?

A. I have an opinion.

Q. And what is the opinion? Should doctors be told to do blood tests based on the current data set?

A. My opinion, and as I stated in my report, is that there are still unanswered questions and they need to be addressed by clinical data, and that data will then answer or address the questions that I have raised.

HARVEY

Q. In the absence of that data, that you believe should exist but does not exist, with the data only as it exists now, should in your opinion Boehringer tell doctors that they should do blood tests for every patient who takes Pradaxa? Yes or no.

MR. MOSKOW: Objection to form.

A. I would object to the language because "should" -- it should be based on data, and although we've had seven years since approval, and we still don't have the data, but the label could be strengthened based upon what we know now, that consideration should be given for these high-risk subgroups, and that testing can be conducted and, you know, there is a belief that there might be some utility. But until the sponsor conducts the studies and we have the data, then we will not know for sure. But there's enough -- a signal is something you then further pursue and --

Q. I have your point that there should be a study.

A. Correct.

Q. My point is just on the current data

HARVEY

set, should there be a recommendation to doctors that every patient should have their blood checked at least once? Yes or no. If you want to say no subject --

A. I -- I --

Q. -- that there should be a study or yes, there should be a study --

A. I -- I --

Q. -- that's fine.

A. I object to the word "should" because that's not how --

MR. SCHMIDT: We're going to be going to the judge on this.

THE WITNESS: Huh?

MR. MOSKOW: Why don't we take a break?

MR. SCHMIDT: Okay.

THE VIDEOGRAPHER: We're off the record at 3:31.

MR. SCHMIDT: Before we go off the record, I am just going to say on the record I've never in my career had a witness who repeatedly objects to questions.

HARVEY
MR. MOSKOW: That's fine.
MR. SCHMIDT: So I appreciate going off the record.
THE REPORTER: We're off the record now.
(Recess taken.)
THE VIDEOGRAPHER: We are back on the record at 3:39.
MR. MOSKOW: Paul, just before we went off the record, you had I think articulated some frustration, and without talking about the import of what you said, I want you to know we did speak with Dr. Harvey off the record. We're -- we believe that there's a disconnect here and Dr. Harvey is trying to be very precise. What we've suggested to him going forward is that rather than say he objects to a way a question has been worded, to suggest that perhaps it be rephrased so he's in a better position to answer it. And we will endeavor to do that going forward.
MR. SCHMIDT: I appreciate that.

HARVEY
And I appreciate that, Dr. Harvey. Let me try to change my question based on what Mr. Moskow just said in discussions.
BY MR. SCHMIDT:
Q. Do you think that the FDA would approve a warning that advised doctors to test blood levels for Pradaxa?
A. Yes.
Q. You do? Okay. So what should that warning say from your point of view, based on the current data? Strike that. Let me try to ask my question differently.
A. Yeah.
Q. Do you think the FDA would approve a warning that said test all patients shortly after they start using Pradaxa to look at their blood concentration?
A. I guess my -- you know, so the clarification that I need is I'm -- I'm having trouble distinguishing the intent versus the wording. And FDA often gives general ranges and then says, you know, practitioners should consider this in your practice based upon

HARVEY
individual patient characteristics. The trend that's been at FDA for many years now has been not to be prescriptive on how to test, but that this is something that should be done and it should be tailored to the individual.
Q. Okay.
A. So that's more what I'm reacting to. So I believe that FDA would write a warning saying that there could be some utility in testing drug levels, how this testing is done should be tailored, and I would believe that they would highlight those patients who were at increased risk because that's where more intensive testing might have the best utility.
Q. So in terms of what we see in Exhibit 9 where it has a preferred test and it has rechecking in one to two weeks, or two weeks later in specific circumstances, do you think the FDA would ever approve --
MR. MOSKOW: Exhibit 15.
MR. SCHMIDT: Exhibit 15. I'm sorry.
A. The -- I think the FDA would want to see data on levels greater than 180 because

HARVEY
they would want to see a justification for that level. But I think the paradigm of rechecking and titrating certainly would resonate with FDA. But obviously there would need to be data submitted in that sNDA to support the various cutoffs.
Q. I might be entirely misunderstanding what you said. I thought you said they didn't tend to endorse specific tests, they didn't intend to endorse specific time frames. Would they -- isn't that inconsistent with what we see in Exhibit 15 where there's a specific test and a specific time frame for rechecking?
A. Well, I don't -- I guess -- please clarify. I had thought that the preferred test would be mass spec LabCorp. That's just sort of an aside that the doctor was giving. I don't think that FDA would ever say, you know, do LabCorp or Quest or whatever. But I think that was just sort of helpful information given that, you know, articles over the years had said well, there was no available test, and now that we know there is.
So I think if I went through step by

HARVEY

step, there would need to be a justification of the 180, but the idea of testing, titrating, you know, after rechecking, and then having data to support the lower dose, which would probably be more defensible based upon the data we have gone over, I think that would all be good. And then with the more traditional FDA language as far as tailoring additional testing based upon the character -- the individual characteristics of the patient.

Q. Apart from the doctor's name at the bottom, in your experience, based on what you understand about the data, would the FDA approve this language for the Pradaxa label as written? Yes or no.

A. Given the data they have, probably no on the 180.

MR. SCHMIDT: Let's look at what I've marked as Exhibit 16.

(Harvey Exhibit No. 16 was marked for identification.)

BY MR. SCHMIDT:

Q. This just reminded me of something I wanted to be sure I covered with you. This is

HARVEY

a list we got yesterday. It says "Additional Reliance Materials" and it's dated November 29. Do you see that?

A. Yes.

Q. Do you understand what this list is?

A. Yes.

Q. What is this list?

A. This list is additional information that was reviewed and is being used today.

Q. Additional information since the time of your report?

A. Yes.

Q. So at the time you wrote your report you did not have this information; is that correct?

MR. MOSKOW: Objection to form.

A. Or if I had the information, since some of this is public information, it wasn't specifically spelled out. And so for clarity and completeness, you know, it was added to this list.

Q. For example, you've got a bunch of websites there. Had you visited those websites at the time you wrote your report?

HARVEY

A. No, I'd not visited those four websites at the time.

Q. Do you have Exhibit 1 in front of you?

A. Yes, I do.

Q. Look with me if you would at page 80. Paragraph 231. Do you see that at the end of the paragraph you say: "I understand that the vast majority of the labs in the U.S., e.g. Quest, LabCorp, are capable of performing the DTT test and the ECT test"? Do you see that?

A. Yes, I do.

Q. Which one is the Hemoclot?

A. Isn't that the -- the DTT?

Q. Okay. So it's your understanding that most labs in the U.S. can perform Hemoclot?

MR. MOSKOW: Objection to form.

A. Could you just clarify how we got from this to that or --

MR. MOSKOW: It doesn't matter.

Q. Just asking a question. Is it your understanding that most labs in the U.S. can perform the Hemoclot?

HARVEY

MR. MOSKOW: Objection to form.

A. As I remember writing this, this was a more generalized view that testing was available in the U.S. And as I read it, I can see that there was some confusion that that then meant that all of these were -- could be conducted all over the U.S. since -- go ahead.

Q. Is ECT a valid assay in your view?

A. Yes.

Q. Is it true that the vast majority of labs in the U.S. can perform either the Hemoclot or the ECT in your view?

A. I don't know if I could say the vast majority could perform them, but my understanding was these tests were available.

Q. Is this -- let me just ask you, is this a true statement in your report, that, quote, the vast majority of labs in the U.S. are capable of performing Hemoclot or ECT? Is that a true statement?

A. Based upon my understanding, yes.

Q. That's where I wanted to go with Exhibit 17. You had not reviewed the Quest website or the LabCorp website. Where does

HARVEY

that understanding come from?

A. Well, I hadn't reviewed these specific websites. It doesn't mean I hadn't gone on the web to look up to see what they -- I could order.

Q. Where did your understanding come from?

A. From the web, and I needed to -- I wanted to document the specifics, and so that's why we added that to the additional material.

Q. So when you surveyed the vast majority of labs, how long did you spend looking at that on the web?

A. Well, I can see I didn't reference it.

Q. Right.

A. So the point of that statement was that this testing is available if one wanted to do it.

Q. Do you know it's true? Did you do the work to make sure it's true that the vast majority of labs have those tests? Or were you guessing?

A. I guess my question to you would

HARVEY

be -- or my clarification would be what is the adequate amount -- if I go to a website and see that I could order it from the U.S., is that enough? Or do I have to actually order it to see if that's doable? So in my -- in the context of my report, I wanted to show that there were options available other than what might be under FDA's purview. There are many tests that are available in these labs that aren't specifically, you know, FDA-approved tests, and there isn't availability, and this was intended just to say that that was the case.

Q. You say the vast majority of the labs in the U.S. have this test; right?

A. That's what I say.

Q. Do you know if that's true? Did you do the work to determine whether that's true? Yes or no.

A. I did a search on the web and found evidence that the tests were available.

Q. Move to strike as nonresponsive. Do you know if it's true, have you done the work to determine that it's true that the vast

HARVEY

majority of labs in the U.S. have these assays? Yes, no or --

A. I thought I had.

Q. Okay. Do you think you have now, sitting here now?

A. Well, I -- by adding these extra references, that provides the different details where one can see what can be ordered. And I think -- I think the intent of my statement stands that if someone wanted to test, they could get their samples tested.

Q. Is that a six-line way of saying yes, that you think that's still a true statement sitting here now?

A. I think this is --

MR. MOSKOW: Objection to form.

A. I think this is still a true statement.

Q. Thank you.

Do you know what a narrow therapeutic index drug is?

A. Yes, I do.

Q. Is warfarin a narrow therapeutic index drug?

HARVEY

MR. MOSKOW: Objection to form.

A. Well --

Q. Yes or no.

A. It doesn't --

MR. MOSKOW: Or can't be answered yes or no.

MR. SCHMIDT: Okay.

A. It doesn't meet --

Q. Can you give one of the three answers that all the lawyers in the room have suggested? Yes, no, or I can't answer yes or no.

A. So the clarification is --

MR. MOSKOW: Just --

A. No, because "narrow therapeutic index" gets used in the context of functionally, but then there is also a regulatory definition of whether or not it's on the list. And although Pradaxa is not defined as a narrow therapeutic index, Bob Temple and others at FDA have called it a narrow therapeutic window product, because although it's not on the official list, it acts as if it was a narrow therapeutic drug.

HARVEY

So if it's from the list, it's -- it's -- there is a list that's incomplete but that's in the regulation and it may not meet that definition, but, you know, Coumadin and the other anticoagulants all have characteristics of narrow therapeutic indexes.

MR. SCHMIDT: I'm going to note for the record that we will be asking either to strike the witness as a witness or for more time with the witness. I'm just looking at the answers. We have had multiple-paragraph answers to simple yes-or-no questions. We have literally had the witness argue with his own lawyer about the need to answer a question yes or no. So let me try to answer my question.

MR. MOSKOW: Let me respond to that first, because we've taken a number of depositions, including recently of Herr Professor Dr. Dr. Barner, who refused to answer any question about risk without also talking about benefit. And, you know, counsel have worked hard together.

HARVEY

I don't mind taking a 30-second break to discuss how to answer a question like the one just posed with the witness so that will aid things. But I don't think there's anything about Dr. Harvey's presentation here that in any way rises to any kind of deliberate obstruction of your ability to get answers.

MR. SCHMIDT: I will note that I believe we gave you extra time with Dr. Barner.

MR. MOSKOW: Give me 30 seconds.

MR. SCHMIDT: Let me just see if I can answer, and if not we'll break.

BY MR. SCHMIDT:

Q. There is a regulatory definition of a narrow therapeutic index drug; right?

A. Yes.

Q. There's a list of them; right?

A. That's correct.

Q. Is warfarin on that list?

A. I don't remember if warfarin is officially on the list. I know Pradaxa is not.

Q. What qualifies something to be on the

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list?

A. The list was created by FDA based upon some characteristics of the drugs that at too high or too low a dose, they could have harm in either direction. And I actually was at the advisory committee where this was discussed, and those older FDA individuals pretty much described how it was an empiric definition based upon their experience.

Q. Okay. And is any NOAC on the list of narrow therapeutic index drugs?

A. My understanding is no, because they're newer drugs and this is an older list.

Q. Am I correct that the list of narrow therapeutic drugs is -- is relatively short?

A. That's my understanding as well.

Q. For example, well under 1 percent of all approved drugs in the United States are on the narrow therapeutic index drug list; right?

A. That's my understanding.

Q. What is an SMPC?

A. Can you provide a context?

Q. Do you know what an SMPC is?

A. Can you provide a context?

HARVEY

Q. Do you know without me giving you a context?

A. Can you provide me a context?

Q. Can you tell me what an SMPC is without giving you a context? I'm about to give you a context.

A. Okay.

Q. Can you tell me without it?

A. At this point, I need a little context for the acronym.

Q. Do you know what a CCDS is?

A. The core data sheet?

Q. Yes.

A. Yes, I know what that is.

Q. Do you know what a summary of product characteristics is?

A. I know about the summary of safety and effectiveness, and I know about summaries of the product. I don't necessarily use that acronym.

Q. But do you know what a summary of product characteristics is?

A. Yes, I do.

Q. That's the European version of the

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label; right?

A. That's my understanding, yes.

Q. And you cite both language from -- and you've done that today in our deposition -- language from both the Pradaxa SMPC and the Pradaxa CCDS; right?

A. Yes, I have.

Q. Did you review the full CCDS and the full SMPC?

A. No, I didn't.

Q. You only looked at parts of them.

A. That's correct.

Q. For example, you quote language from both about references to monitoring. Do you remember that?

A. That's correct.

Q. Did you look at both the SMPC and the CCDS to see if they contain the company's views as to when monitoring should be done?

A. That wasn't the focus of my review. The focus was the difference between the core data sheet, the European label, and the difference with the U.S. label. That was the focus of my review.

HARVEY

Q. You know that there's different warning standards in Europe versus the U.S.; right?

A. Yes, I do.

Q. For example, I've heard regulatory folks say that the FDA's more data driven than EMA, the European version of the FDA. Have you heard that?

A. I have heard that --

MR. MOSKOW: Objection to form.

A. I've heard their standards are different.

Q. Do you know how they're different?

A. They operate under a different system. It's not a centralized system. They have rapporteurs and co-rapporteurs, and there's variability on the risk tolerance of the various reviewers.

Q. Are you aware of the FDA requiring -- being more demanding that there be data to support labeling language than EMA?

MR. MOSKOW: Objection to form.

A. I find that the more experience I've gotten in the regulatory space, the more

HARVEY

difficult it is to pigeonhole one agency or another as data-driven or not.

(Harvey Exhibit No. 17 was marked for identification.)

BY MR. SCHMIDT:

Q. Marked as Exhibit 17 is a copy of the Pradaxa SMPC. Do you see this?

A. Yes.

Q. And actually at page 34 of your report, Exhibit 1, you quote language from the SMPC about how the measurement of dabigatran-related anticoagulation may be helpful to avoid excessive high exposure to dabigatran; correct?

A. Yes.

Q. Did you look in this document to see if the SMPC contains any guidance to see whether the guidance -- the SMPC gives any guidance as to when that monitoring may be useful?

A. And as I say, when I did my review, I was looking for differences and did not go into depth on what -- on what was there in the Europe versus what was not there in the U.S.

HARVEY

Q. Is that a different way of saying no, you didn't look to see if the document contains guidance as to when that coagulation testing should be done?

MR. MOSKOW: Objection to form.

A. Given the length of the document, the focus of my review was to look at differences between this and the U.S. label and similarities to the core data sheet and which was different from the U.S. label.

Q. Let me ask the question very specifically and very focused.

Did you look in the SMPC to see if the SMP specifies when anticoagulation testing is recommended? Yes or no.

A. No, I did not look specifically for that.

Q. Look at page 67, if you would. If you look at the bottom of the page, the last paragraph, the second sentence of the last paragraph is the one we have been discussing: The measurement of dabigatran-related anticoagulation may be helpful to avoid excessive high exposure.

HARVEY

Do you see that?

A. No, I don't. Which paragraph?

Q. The last paragraph on the page.

A. Uh-huh.

Q. The second sentence on the last paragraph. Do you see that sentence I just read?

A. "However"? Okay, yes.

Q. That's the sentence you quote in your report; right?

A. Yes.

Q. Read the sentence right before that, please.

A. "Pradaxa does not in general require routine anticoagulant monitoring."

Q. Do you agree with that statement from the SMPC?

A. And as I said before, I have -- I distinguished between monitoring and post, you know, testing for dose adjustment.

Q. Okay. So with that distinction, do you agree with that sentence?

A. I agree with that sentence.

Q. Okay. Let me just see if I can round

HARVEY

out those questions I was asking you earlier.

Mindful of your point that there should be further study, does the data as it exists now support a labeling recommendation to doctors that every patient who takes Pradaxa should have their blood checked at least once? Yes or no.

A. Not having seen all the data, I think the data warrants being submitted to FDA for them to evaluate that.

Q. Okay. From the data you have seen in your 200 hours of work, is such a labeling recommendation warranted, that every patient should have their blood levels checked at least once just based on the data as it exists now as you've seen it?

MR. MOSKOW: Objection to form.

Q. Yes or no or you can't say?

A. I think -- I think that it's reached the threshold for that to be included in the label. But, as I'd said, there's more work that the sponsor needs to do to provide additional data for clarity and refinement of that.

HARVEY

Q. Just yes or no. Does the data as it exists now support the specific recommendation that the broadest range patient should be in is 50 to 150? Yes or no.

A. Yes.

Q. Okay. Look with me, if you would, at page 68 of Exhibit 17. Do you see there's a heading called Surgery and Interventions?

A. Yes.

Q. Do you see that in the third paragraph, they talk -- they say caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted?

Do you see that?

A. Yes, I do.

Q. And so that's one situation where anticoagulant monitoring might be appropriate when someone is discontinuing for surgery; correct?

A. Correct.

Q. Had you seen that before I showed that to you?

A. I've seen similar wording elsewhere,

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yes.

Q. Had you seen it in this document before I showed it to you?

A. I hadn't seen it in this specific document, but --

Q. Okay. Look with me, if you would, at page 80. There's a heading titled Overdose. Do you see in the second paragraph it talks about in case of an overdose suspicion, coagulation tests can help to determine bleeding. Do you see that reference to using coagulation tests?

A. Yes.

Q. That's another instance where coagulation tests might be helpful in terms of assessing Pradaxa patients; correct?

A. That's correct.

Q. You had not seen that language in this document before I showed it to you; correct?

A. Actually, I have seen that because the DTT test is available in the U.S. and would have some utility for U.S. prescribers were it in the U.S. label.

HARVEY

Q. The DTT test is available in the United States?

A. Oh, excuse me. I was thinking of the APTT. No, I correct myself. I'm sorry.

Q. Would the APPT test have some utility in measuring anticoagulation?

A. There is evidence that a extremely high APTT is informative and can be used regardless of what reagent. If it's off the scale, then that indicates a concern.

Q. Other than when someone is stopping the medicine on an emergency basis for some kind of surgery or when they've had an overdose of the medicine, is there anything you can point me to in the SMPC where the company recommends using anticoagulation tests?

A. I think we established that I didn't study the entire document on Europe. I looked for differences between the European document and the U.S. FDA document so I would have to answer no.

Q. Move to strike everything other than "no." Can you point me -- did you see any instances in the company core data sheet where

HARVEY

specific use of the -- of an anticoagulation test was recommended outside of the context of something like an overdose or emergency surgery?

A. In the -- I think in the context of renal insufficiency, wasn't that the table 13 that we talked about before? I would have to look at the core data sheet.

Q. Let's mark the core data sheet.

Okay, while we're doing that, are you aware that both the SMPC and the company core data sheet have been submitted at various points in time to the FDA?

A. I am -- I have heard that. I don't know whether those were submitted to the IND or as an annual report.

Q. You know that they were submitted at various points in time; correct?

A. That's what I have heard.

MR. SCHMIDT: Okay. Exhibit 18 is the company core data sheet. Is it 19 or 18?

MR. HAILEY: 19. 18.

MR. SCHMIDT: 19. Let's mark the

HARVEY

company core data sheet.

(Harvey Exhibit No. 18 was marked for identification.)

THE REPORTER: What number are we marking for the record?

MR. SCHMIDT: We're marking Exhibit 18, the company core data sheet.

BY MR. SCHMIDT:

Q. What section were you referring to, doctor?

A. Can you ask the question again?

Q. Yeah. I thought you just referenced a table 13 from the company core data sheet that you wanted to look at. Is that what you referenced a moment ago?

A. Yes.

Q. Does that include plasma concentration data?

A. Can you repeat the question? I thought you were talking about renal issues.

Q. No. Does table 13 include plasma concentration data?

A. No, it doesn't.

Q. Is there anything in the company core

HARVEY

data sheet that speaks to use of anticoagulation testing that you have seen outside of the context of emergency surgery or overdose or something like that?

A. No, it does not.

Q. And, in fact, the company core data sheet contains the same statement that we saw in the SMPC with which I think you said you agree, that Pradaxa treatment does not require anticoagulant monitoring on page 10.

A. Correct.

Q. Have you studied the regulatory record -- you've talked at various points in time about distinctions between the European label and the U.S. label; right?

A. Yes.

Q. Is it your opinion that any time information is included in the European label it must be included in the U.S. label?

A. Can you rephrase "must"? So are you saying that there must be simultaneous submissions between EMA and FDA?

Q. No, I'm asking something a little different.

HARVEY

Is a U.S. label automatically automatic -- automatically inadequate simply because it does not include some piece of information included in the European label?

A. I --

MR. MOSKOW: Objection to form.

Q. Or does the substance of the information the basis for the information matter?

A. Nothing is automatic in regulatory.

Q. Okay.

A. And if something is in the European label which helps practitioners use it more safely, then that's something that should be submitted to the U.S. label.

Q. Before you made the determination that information in the European label should also be in the U.S., label would you want to understand the data that supported it and the reason that it was added to the European label?

A. Yes, I would.

Q. Have you made that survey -- you've noted various distinctions between the European label and the U.S. label in this case.

HARVEY

In all those instances, have you made a point of looking at the underlying data that supported the European labeling and the regulatory interactions that led to the addition of that language to the European labeling?

A. No, I have not.

Q. Have you done that in any instance?

A. Can you clarify?

Q. Sure. In any instance of language that you believe is in the European label but not the U.S. label, have you made a point of looking at the data that justified the European label and looking at the regulatory interactions that resulted in the European label?

A. No.

Q. Okay. You understand that a company core data sheet is intended to be a basis for a company's worldwide labeling; right?

A. Correct.

MR. MOSKOW: Objection to form.

Q. And you understand that many companies have procedures that, when material

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appears in the company core data sheet, they have an obligation to request a label change to include that same material in their U.S. label?

A. Correct.

Q. In the instances where you say there's material in the Pradaxa core data sheet that is not in the U.S. label, have you reviewed -- strike that.

In fact, are you familiar that some companies have actual formal documentation processes -- sometimes they call it exceptions and things like that -- where they will make note of differences between the U.S. label and the company core data sheet and confirm that they've tried to get those parts of the company core data sheet put in the U.S. label?

MR. MOSKOW: Objection to form. You can answer.

A. I'm familiar with that in some companies. I can't say with all companies.

Q. Do you know if Boehringer has a process where -- strike that.

Do you know if Boehringer has a policy or a practice that if something is in

HARVEY

the company core deteriorate they will try to get it added to the U.S. label?

A. I don't know of that specific policy.

Q. Do you know for the instances of items you say are in the company core data sheet but not the U.S. label whether Boehringer did, in fact, in every one of those instances try to have those -- that relevant language added to the U.S. label?

Have you done the review of the regulatory interactions to confirm or refute that?

A. I have reviewed the interactions between the sponsor and FDA and I did not find instances where -- or at least I did not find evidence that all of those had been submitted in sNDAs. They may have been submitted to other parts of FDA, but not actually as an sNDA for a labeling change.

Q. Can you tell me any provision, any language that you think is in the core data sheet that should be in the U.S. label that Boehringer did not submit to the FDA and request that it be added to the U.S. label?

HARVEY

A. Not off the top of my head.

Q. Do you know if any such language exists?

Is there any such language that appears in the company core data sheet that does not appear in the U.S. label but that you think should appear in the U.S. label that Boehringer never submitted to the FDA, that you know Boehringer never submitted to the FDA?

A. I would have to refer to my report, so page 25. I'm not sure how much depth I want to go into because I don't want to be repeating past conversations.

Q. Yeah.

A. One -- the big example, of course, is the 110 dose.

Q. Okay.

A. That was submitted. It was rejected. FDA gave a path for -- in 2011 on what the sponsor needed to do in order to get the 110 dose approved for the A-fib indication, and here we are in 2017 and it still has not been done.

Q. You know that Boehringer wanted the

HARVEY

110 approved; right?

A. Yes.

Q. And you know they made multiple efforts to get it approved, at least four that you cite in your report; right?

MS. PRESBY: Objection.

Q. Is that true?

A. The issue is whether or not the sponsor provided the data that FDA requested that FDA outlined as the path forward.

Q. Is it true that Boehringer made four separate attempts that you're aware of to get approval of the 110 dose?

A. Yes.

Q. Spanning from 2010 or before 2010 all the way to 2015?

A. Yes.

Q. And you say that a path forward was given. That would have involved some kind of unspecified study; correct?

A. It would have been -- involved a study, and FDA outlined what should be included in the study.

Q. Have you -- have you come up with a

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design of what that study might look like to determine if it would be feasible in the real world?

A. I -- I agree with how FDA outlined that study moving forward, and it's my understanding that that study has not been done or even attempted.

Q. Move to strike as nonresponsive. Have you attempted, looking at the guidance that the FDA, gave to evaluate what the design of that study would look like and how large it would need to be in order to determine if it were feasible?

MR. MOSKOW: Objection, asked and answered.

A. Yeah, I -- I have not.

Q. Have you seen in the documents where anyone comes up with a feasible design for such a study that could be run in the real world?

MR. MOSKOW: Objection to form.

A. I guess I'm having trouble with "feasibility" because in my experience in FDA, when companies say something's not feasible, it usually means that it's expensive, and yet when

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it's in their best -- best interest, then the studies get done.

So feasibility is something that's very difficult to define in the regulatory sense. The FDA made the proposal, and I think it's a -- it's a valid proposal, that was their recommendation on the path forward. Submitting data four times that didn't address their concerns, to me, is not a genuine attempt to try to get it approved.

Q. Move to strike as nonresponsive and note that we've got another one-page answer to a question I didn't ask.

My question simply is, sir, is have you seen documentation about what this study might look like that lets you say with a reasonable degree of professional certainty in your opinion that it would have been feasible?

A. No, I --

MR. MOSKOW: Objection to form.

A. I -- I've not looked at those details.

Q. Now, would you agree with me that you shouldn't submit speculation to the FDA?

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MS. PRESBY: Objection, form.

A. Can you define speculation, since that was a problem -- it's a term I should not have used because I used it in a traditional vernacular sense. Again, as I'm hearing you say it, it sounds like there's a legal context that I didn't consider. There's not -- I'm using --

Q. In the way you use it, you don't even need to define it because I think I know what you mean. In the way you used the term "speculation," should companies submit speculation to the FDA?

MR. MOSKOW: Objection to form.

A. Well, and as I think about how I --

Q. Yes or no.

A. They should not submit speculation.

Q. Okay. Should -- if a company -- you understand that when you create a model of some sort it involves making certain assumptions and trying to make predictions based on data; correct?

A. Correct.

Q. And there's sometimes -- and you can

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test your model to see whether it's validated; right?

A. Correct.

Q. And sometimes when you test your model, it works pretty well and it's validated; right?

A. Correct.

Q. And sometimes you test your model and you come to the conclusion that didn't work, it's not validated?

A. Correct.

Q. And there could be any number of reasons why your model's not valid; correct?

A. Correct.

Q. Could be because you made wrong assumptions; right?

A. Correct.

Q. It could be because your data set wasn't representative; correct?

A. Correct.

Q. Could be there's just something you didn't anticipate; right?

A. Uh-huh, correct.

Q. If a company does a model and is not

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able to validate their model should they submit a nonvalidated model to the FDA?

A. Yes, they -- they may still submit it because the evaluation of the model can have various interpretations, and validation can have -- there could be various levels of validation.

So even though it's not reached the highest level of validation in the eyes of the company, there still might be utility.

Q. There might be utility, but are they required to submit it in your view under the regulations?

A. If it's significant, if it has significant impact on how a product could be used, then yes.

Q. By definition does it have significant impact if they can't validate it?

A. It depends. In -- I think we've established I'm not an expert on modeling.

Q. Okay.

A. But I -- I would like to correct my previous statement, because of course since modeling is based upon data, then it truly

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isn't speculation, it's --

Q. I wasn't --

A. I wouldn't -- I -- that word is -- you know, that was inappropriate use of the word.

Q. I don't think you used it with respect to the model, but that's fine.

If a company does a model and they're not able to validate it and they come to the view they can't validate it because the model doesn't work, for one reason, for multiple reasons, are they under an obligation to say, hey, we did this model, it didn't work, here you go, FDA?

A. Well, but --

Q. Would this be --

A. -- in any case, they should submit it because part of the model was the basis of the calculation of the doses for the pediatric study.

Q. Is it your testimony under oath, sir, that Boehringer used its dose titration model as the basis for the pediatric dosing?

Is that your testimony?

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MR. MOSKOW: Objection to form.

A. It's my understanding from the documents that I read that some of the information from that modeling exercise that was not submitted then informed the process of the pediatric study. I've read that in some of the documents.

Q. I'm asking a general question.

If a company creates a model and decides the model's not valid, that it doesn't work, that it's flawed, do they have an obligation to submit it?

MR. MOSKOW: Objection to form.

Q. Yes or no.

A. If it -- if the model raises issues of safety concern, then there's nothing stopping the company from submitting it to FDA.

Q. Move to strike as nonresponsive. How about you answer my question, please, sir?

My question is if a company conducts a model and they conclude that it's not valid, that it doesn't work, do they have a requirement to submit it to the FDA? Yes or no.

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MR. MOSKOW: Objection to form.

A. It really would depend on the particulars of what they were finding. It's hard -- I cannot give a yes or no answer because it's too general of a question.

Q. Might be yes, it might be no, depending on the facts; correct?

A. Correct. In this case, it's --

Q. I'm not asking you about this case yet. Do -- do you know, did the FDA do modeling of dose -- of plasma concentrations?

A. We talked about that this morning. You said they did.

Q. Do you know if they did?

A. I -- all I would know is what I read in the documents. There were some references to them.

Q. Do you know if they did? Yes or no.

A. I don't know if they did. There were references that they did.

Q. Do you know -- as to the modeling that Boehringer did, do you know -- could you replicate Boehringer's models yourself?

A. Not being an expert in modeling, no,

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I couldn't.

Q. Do you know what variables they controlled for?

A. No, I don't.

Q. Do you know if the patient data used in the model was representative of the overall patient data set?

A. I don't know the specifics.

Q. Is that an important fact, that the patient data used in the model be representative of the overall patient data set?

A. Yes. I would have hoped they would have done that.

MR. SCHMIDT: Why don't we take a break and change the tape.

THE VIDEOGRAPHER: We're off the record at 4:25.

(Recess taken.)

THE VIDEOGRAPHER: Here begins media number 5 in the video-recorded deposition of Dr. Brian Harvey. We're back on the record at 4:35.

BY MR. SCHMIDT:

Q. Doctor, have you evaluated the

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efforts that Boehringer made to validate their dose titration model that we have been discussing all day?

A. I -- I've reviewed the documents and in general have looked at that.

Q. Do you understand that part of what they did was they took their model and they said, here's what our model predicts in terms of bleeding versus stroke, here's what we see in the real world, do those track up?

A. I understand that, yeah.

Q. What did they see when they did that?

A. My understanding is, is that they felt that there was no monitoring required because of things holding up, as you say.

Q. Let me try to ask my question a little more precisely.

When the scientists at Boehringer compared their predicted results from the model to the actual real-world results did they see meaningful differences between them?

A. I -- I can look back, but I remember that they found that there were -- the results were similar.

HARVEY

MR. SCHMIDT: Let me show you a document.

(Harvey Exhibit No. 19 was marked for identification.)

BY MR. SCHMIDT:

Q. I've marked as Exhibit 19 a manuscript form of the exposure paper that we were talking about earlier.

Do you recognize this, just in a different format?

A. In a different format, yes.

Q. And the reason I marked it in a different format is because this has certain tables attached to it that I think were published online but that were not, for space reasons, part of the journal article.

A. Okay.

Q. I'd like to ask you to look at table 15, please.

Before you do, did you understand the 2014 exposure paper from Dr. Reilly to be Boehringer sharing their -- the results of their modeling with the scientific community?

A. I had thought that that's how you

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presented the paper.

Q. Is that your understanding of what the paper does?

A. That's my understanding.

MR. MOSKOW: Can I just ask you to identify which is table 15?

MR. SCHMIDT: Oh, I'm sorry. It might not even be table 15 it's not table 15, it's Exhibit 15 from the Reilly deposition, so let me ask my question differently.

Q. If you look at the back of Exhibit 19 there are tables attached to it.

A. Yes.

Q. And if you go about four pages in, there's a table with some text above it that says "Variables in the final logistic regression model"? Yeah, right there on your right-hand side. Do you see that?

A. "Variables in the final logistic regression model."

Q. Right. Have you seen this before?

A. Like, not in this format, but I don't know if I've seen this specific table or this

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analysis.

Q. Do you know that this is referring to the dose titration modeling you talk about for pages and pages in your report?

A. Yes.

Q. And do you know what those variables that they used were in the final logistic regression model?

A. Are you saying based upon this table or --

Q. Independent of this table. Have you independently looked at that?

A. No, I haven't independently looked at it.

Q. Bottom half of the page, there's a chart that says at the very bottom Predictive Value Analysis.

Do you see that?

A. Yes, I do.

Q. And do you know what that means?

A. No, I don't.

Q. Okay. It has in the key a square for predicted and a star for observed. Do you see that?

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A. Yes.

Q. And then it's got a grouping on the left for major bleed and a grouping on the right for stroke SE.

Do you see that?

A. Yes, I do.

Q. And if you look at it, there's some instances where the square that says predicted is very close to the star.

Do you see that?

A. Yes.

Q. And there's some instances where the star is well outside the -- not just well removed from the square but well outside the confidence interval around the square. Do you see that?

A. Yes, uh-huh.

MR. MOSKOW: Objection to form.

Q. Do you know what this data represents?

A. No, I don't.

Q. Do you know that there were multiple instances where when Boehringer -- strike that.

Do you know that this is, in fact,

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Boehringer's efforts to say here's what we predict from our model. How does that compare to what we see in the real world?

MR. MOSKOW: Objection.

Q. Do you understand to be what this chart is measuring?

MR. MOSKOW: Objection to form.

A. That's how you've explained it to me.

Q. Do you know that what I've said is true or not true?

A. I don't know. I don't have a independent validation to confirm or deny what you're saying.

Q. Okay. And, for example, if you look at the -- if I have described it accurately, if you'd look at the category of Major Bleed, you will see that at the high levels, 9 and 10, the observed rates of major bleed are much higher than what was predicted in the model. Do you see that?

A. Yes.

Q. And if you look at stroke at the high rates, the rates of stroke are lower than what was predicted in the model; right?

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A. Yes.

Q. So my question to you, is if I tell you that, in important groups, the model underpredicted actual bleeds and underpredicted stroke benefit, do you know if that's true or not?

A. In general --

MR. MOSKOW: Objection to form.

A. -- no, no, I don't. But I think there are alternative interpretations.

Q. Do you -- do you -- let me ask you this. Do you have an opinion about how accurate the model was when the scientists compared what was predicted under the model to what was seen in the real world? Do you know how accurate it was?

A. I wouldn't be able to tell.

Q. Okay. Let me show you a few more documents on this point.

A. Clarifying question. Was the model based upon the first generation product and the observed based on the first or the second?

Q. Do you know?

A. I don't know.

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Q. You're familiar with some of the discussions that Boehringer had with EMA on questions regarding dose titration and modeling and plasma concentration?

A. I saw references to those. I did not study those in depth.

(Harvey Exhibit No. 20 was marked for identification.)

BY MR. SCHMIDT:

Q. Have you seen the document I've marked as Exhibit 20 from the European Medicines Agency, the European FDA?

A. It's my understanding that this document was available to me, but I have not studied it.

Q. Okay. I'm going to just point you to some of the language in this. Look with me if you would at page 16. Actually, look at page 15, if you would. And if you look about halfway down, you'll see some italicized language where they say the MAH is requested to provide more details.

Do you see that?

A. Yes, I do.

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Q. Who's the MAH? Is that a term you're familiar with?

A. No, I'm not.

Q. I'll represent to you that the MAH stands for Market Authorized Holder, which is Boehringer.

With that context, do you understand this to be EMA asking Boehringer to provide more details?

A. Yes.

Q. Then do you see Boehringer's response is printed below?

A. Uh-huh.

Q. And I'd like to carry you over to the next page, to page 16. There's a paragraph that begins "As a result." I'll read it, but tell me when you get there.

A. "As a result"?

Q. Yes. "As a result, BI has concluded that the trial simulations based on the PK response model that were made in 2012 have limitations."

Did I read that correctly?

A. Yes.

HARVEY

Q. So this is talking about the same dose titration model we have been talking about; correct?

A. Correct.

Q. And BI is telling the European Medicine Agency that they believe that the trial simulations based on the model have limitations; correct?

A. Correct.

Q. And they were unable to predict the dose/response difference between 110 milligrams bid and 150 milligrams bid seen in RE-LY.

Did I read that correctly?

A. Yes, you did.

Q. Do you know whether that's a true statement, an untrue statement, or do you not have a view?

MR. MOSKOW: Objection to form.

A. I do not have a view.

MR. SCHMIDT: Okay. Let me show you another document. And I will represent to you that this is a Boehringer submission to EMA that was made in advance of Exhibit 20.

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(Harvey Exhibit No. 21 was marked for identification.)

BY MR. SCHMIDT:

Q. I'll ask you to look -- tell me, have you seen this Boehringer submission that I've marked as Exhibit 21?

A. To clarify, submission to EMA?

Q. Yes.

A. Yes.

Q. Have you seen that before?

A. I have not studied this specific document since my focus was U.S. FDA and that's my main area of expertise.

Q. If you look through this, this document is called Simulation Analyses and Validation. That's the heading.

Do you see that up at the top?

A. Yes, I do.

Q. And if you look through it, on page 4 it talks about validation of the trial simulation approach.

Do you see that?

A. Yes, I do.

Q. This says validation step 1,

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validation step 2 on page 5, and validation step 3 on page 7.

Do you see that?

A. Yes, I do.

Q. Look with me, if you would, at the paragraph above -- on page 7 above validation step 3.

"Altogether, given the totality of evidence that was included in the RE-LY trial, the discrepancies between predicted and observed outcomes were regarded as major."

Did I read that correctly?

A. Yes, you did.

Q. "The approaches used in this validation step raised doubt concerning the model conclusions."

Do you see that?

A. Yes, I do.

Q. Do you understand that to be a true or a false statement, or you don't know, that when -- that the discrepancies between predicted and observed outcomes using the model we have been discussing were major?

MR. MOSKOW: Objection to form.

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Q. True or false or you don't know?

A. I don't know.

Q. On the next page, they talk about -- if you look under the table there you'll see they reference a PK set and a nonPK set.

Do you see that?

A. Yes, I do.

Q. And is that consistent with your knowledge?

And then in the next paragraph, they say they had a large PK set, about 70 percent, whereas the nonPK set was about 30 percent.

Do you see that?

MR. MOSKOW: Objection to form.

A. I --

Q. Is that consistent with your knowledge that in about 70 percent of RE-LY patients, they had plasma concentration data and about 30 percent, they didn't?

A. Yes, that's consistent with what I reviewed in the documents.

Q. They say: "Although the PK set was large, 70 percent, it was not representative for the outcomes in the total RE-LY

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population."

Did I read that correctly?

A. Yes.

Q. Do you know if that's a true or untrue statement?

A. That's the first time I'm hearing that.

Q. Okay. Do you know if it's true or false or you don't --

A. I don't know if it's true or false. I'm surprised by it, though.

Q. They say: "Whereas the nonPK set -- the -- the PK set represented a somewhat positive selection whereas the nonPK set represented a somewhat negative selection."

Do you see that?

A. Yes, I do.

Q. Do you know if that's true?

A. No, I don't.

Q. Okay. But you understand what they're saying, that they're expressing concerns that the data they have from the PK set is not representative of the data from the overall study; correct?

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MR. MOSKOW: Objection.

A. Correct.

Q. That's a potential concern; right?

A. Yes.

Q. Then they go on to say: "In summary, the attempted internal validation of the model predictions and trial simulations by using the RE-LY trial data could not successfully validate the proposed three-dose dabigatran titration scheme with plasma concentration cutoffs where based on optimization for one NCB definition."

Do you see that?

A. Yes.

Q. Do you know if that's a true or false statement, that they could not successfully validate the proposed three-dose dabigatran titration scheme?

A. I have no knowledge if that's true or not.

Q. Go back with me, if you would, to Exhibit 20. This is the EMA document. We were on page 16. Look with me if you would at page 16. You remember we were looking at the

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write-up that BI had provided to the EMA?

A. Yes.

Q. Below that is the EMA's assessment. Do you see that?

A. Starting with which -- oh, yes, assessment, yes.

Q. And they've got their own boxed assessment before they ask their next question.

Do you see that?

A. Yes, I do.

Q. And I want to focus on the last question: "The MAH concludes that trough -- that through dose recommendations for SPAF according to the current label, an optimization of the efficacy and bleeding profile of dabigatran etexilate is already achieved compared to warfarin and/or dabigatran 150 as the reference dose."

Do you see that?

A. Yes, I do.

Q. Here's the part I want to focus your attention on: "The MAH" -- and that's Boehringer; right?

A. Correct.

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Q. "Boehringer does not believe that available data such as the PK response model support that routine monitoring of dabigatran anticoagulant activity would result in an enhanced balance between benefits and bleeding risks. This is endorsed."

Did I read that correctly?

A. Yes, you did.

Q. Do you agree with that statement from Boehringer that available data such as the PK response models support that routine monitoring would result in an enhanced balance between benefits and bleeding risks?

MR. MOSKOW: Objection to form.

A. No, I don't agree.

Q. Okay. You see where the EMA agrees, though, right, where they endorse that proposition?

A. Yes.

Q. So you disagree with EMA on that?

A. I disagree with EMA on that based upon some of the information I saw in the records.

Q. Okay. Look with me, if you would at

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page 66, please.

By the way, do you see this article at the beginning, this EMA document at the beginning cites certain allegations made in a BMJ article, for example, on page 5?

Do you see that?

A. Yes.

Q. And you cite that BMJ article in your report; correct?

A. Yes, I do.

Q. Are you aware that that BMJ article was only published after plaintiff's lawyers took selected documents from Boehringer and fed them to the author of that article?

MR. MOSKOW: Objection to form.

A. Can you clarify "fed"? Fed them?

Q. I don't know how it was passed, if it was under the table, if it was by email, if it was in a bar, but gave them selected documents from Boehringer that they then wrote about.

MR. MOSKOW: Objection to form.

A. I heard that there were some questions about how the cases were determined, you know, were -- were obtained but not that

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the -- that undermined the validity of each individual case.

Q. I may be asking a different question. Are you able to rule out -- did you know that there were interactions between plaintiff's lawyers and the BMJ author before the BMJ author wrote her piece?

A. That was not something I was aware of when I originally read the article.

Q. Were you aware --

A. I've since heard -- I've since heard it and seen it on the web that those allegations were made.

Q. What have you heard?

A. I heard -- it was what I read on the web, that there was an interaction between lawyers and BMJ. And I've also read that, you know, the, you know, the interaction doesn't negate the validity of any individual case just like simulation of reports to FDA MedWatch. If it's simulated and it's a real report then it's still a real report.

Q. What did you read on the web about the nature of the interactions between the

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plaintiff's lawyers and the BMJ article?

A. I didn't read anything specific.

Q. No, I --

A. I just knew that there was an accusation. It was a summary article.

Q. Do you know if the BMJ article was ghostwritten by plaintiff's lawyers?

MR. MOSKOW: Objection to form.

A. I'm not sure what the definition of ghostwritten means, but I don't know who wrote the article.

Q. Okay. Can you rule out that plaintiff's lawyers contributed to the writing of the BMJ article?

A. I can't --

MR. MOSKOW: Objection to form.

A. Can't rule out anything.

Q. Look with me, if you would, at page 15.

MR. SCHMIDT: Off the record.

(Discussion held off the record.)

BY MR. SCHMIDT:

Q. Look with me, if you would, at page 15. And do you see under 1.5 about five lines

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down it says therapeutic drug monitoring, TDM?

A. I see 1.5.

Q. If I can just point you to it. Do you see right here where it defines TDM as therapeutic drug monitoring?

A. Yes.

Q. Look with me, if you would, at page 66, please. And you will see that the top half of this page falls in one of these assessment sections where it's the EMA writing.

Do you see that?

A. Yes.

Q. Let's look at the second paragraph. EMA writes: "It is considered that currently, the benefit/risk profile of Pradaxa is positive."

Do you see that?

A. Oh, on page 66?

Q. Yes, sir.

A. Okay.

Q. Second paragraph, first sentence.

A. Okay, yes.

Q. Is that a true statement, that the benefit/risk profile of Pradaxa treatment is

HARVEY

positive?

A. Can you clarify what context that is in, based upon the RE-LY data? I --

Q. On the data we know today. Do you believe that the benefit/risk profile of Pradaxa is positive?

A. I -- I can't answer that because it's very general and I would need to know the specifics of the question.

Q. Well, you agree with me that a drug should not be on the market unless it has a positive benefit/risk profile; right?

A. Correct.

Q. Are you arguing that Pradaxa should not be on the market?

MS. PRESBY: Objection.

A. No.

Q. Do you agree with me that Pradaxa has a positive benefit/risk profile?

A. In general, yes.

Q. They go on to say: "The size of the patient populations necessary to enter into studies investigating therapeutic dose monitoring of Pradaxa is regarded as too large

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compared to the theoretical improvement in the benefit/risk profile to justify such studies."

Do you see that?

A. Uh-huh.

Q. Do you agree with that statement?

A. No, I don't.

Q. They go on to say: "Without such studies, the scientific basis for making routine therapeutic drug monitoring recommendations is too weak."

Do you see that?

A. Yes, I do.

Q. Do you agree with the European FDA that without studies, the scientific basis for making routine therapeutic drug monitoring recommendations is too weak?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. Yeah, no, I don't agree with that either.

Q. They go on to say: "It is maintained that coagulation tests," and then they list a bunch, "are useful in situations such as emergency surgery or uncontrolled major

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bleeding as listed in the current SMPC."

Do you see that?

A. Yes, I do.

Q. Do you agree that those are the situations where coagulation tests are helpful: Emergency surgery or uncontrolled major bleeding?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. I agree that that's a subset of where testing should be done.

Q. But not all?

A. Not all. No, I think it's not comprehensive.

Q. And finally, it says, EMA says: "It is agreed that routine therapeutic drug monitoring of Pradaxa should not be recommended."

Did I read that correctly?

A. Yes.

Q. Do you agree with that?

A. And based upon my distinction between routine monitoring and dose adjustment testing, I would -- I would agree with that statement.

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Q. Okay. Look with me, if you would, at page 93 of your report. We're going to talk now about the reversal agent, if that's okay.

On page 93 you talk about the reversal agent; correct?

A. Correct.

Q. And you have some language that I wanted to ask you about. I got the wrong page. Go with me to 92, please. There was a period of time between -- let me just strike that.

There's now a reversal agent for Pradaxa; correct?

A. Correct.

Q. It's called Praxbind; correct?

A. That's my understanding.

Q. It's an incredible product; correct?

MS. PRESBY: Objection, form.

MR. MOSKOW: Objection to form.

A. Can you help me define incredible?

Q. In whatever sense you would use it, do you think it's an incredible product?

MR. MOSKOW: Objection to form.

MS. PRESBY: Objection.

A. It -- it was approved by FDA under

HARVEY

accelerated -- accelerated review and it was a novel BLA and so it was a high priority for FDA's approval.

Q. Do you think it's a highly valuable product?

MS. PRESBY: Objection, form.

A. Yes, I do.

Q. Do you think Pardaxa's a highly valuable product?

MR. MOSKOW: Objection to form.

A. I think Pradaxa has a role in clinical practice, and I think the approval of the reversal agent enhances the benefit/risk of that. And it can be further improved with some of these labeling changes in specific populations.

Q. Before Pradaxa, the only oral anticoagulant was warfarin; correct?

A. Correct.

Q. And warfarin has all kinds of problems with it; correct?

MR. MOSKOW: Objection to form.

A. There are problems, but clinicians know how to manage that. And there are

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Coumadin clinics where it's a highly, highly intense monitoring system.

Q. One of the problems with warfarin is that it has a lot of food interactions that NOACs don't have; correct?

A. That's correct.

Q. And food interactions are a problem because if you take one of those foods while you're using warfarin, it can put you at too much risk of bleeder stroke?

MR. MOSKOW: Objection.

A. That's correct.

Q. Warfarin has an unusually large number of other medicine interactions that can have the same effect in terms of putting you at too high a risk of bleed or stroke?

MS. PRESBY: Objection.

MR. MOSKOW: Object, form.

Q. Correct?

A. That's true.

Q. And warfarin has monitoring challenges with it; correct?

MR. MOSKOW: Object --

A. Correct.

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Q. Routine --

MR. MOSKOW: -- form.

A. Routine --

THE REPORTER: I'm sorry, it's late in the day. There's no space between speakers. Start your question, make your objection, and then the answer. Thank you.

THE WITNESS: And so can you repeat?

MR. SCHMIDT: Sure.

BY MR. SCHMIDT:

Q. Warfarin has monitoring challenges associated with --

A. Yes.

Q. -- it.

MR. MOSKOW: Objection, form.

Q. Okay.

A. Yes, Coumadin has regular monitoring so they -- they have monitoring in the truest sense.

Q. And you understand that warfarin monitoring is problematic for some patients who do not end up using a drug they might not have

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been on because of the monitoring requirements; correct?

MR. MOSKOW: Objection to form.

A. Yes, I understand that.

Q. You also understand that even with warfarin monitoring, a large number of warfarin patients still end up outside the therapeutic range at different points in time?

MR. MOSKOW: Objection to form.

A. Yes, I understand.

Q. For example, do you know here in the United States what the average percentage of time spent by warfarin patients inside the therapeutic range is?

MR. MOSKOW: Object, form.

A. No, I don't.

Q. Would you have any reason to disagree with it being only 55 percent of patients?

MR. MOSKOW: Objection to form.

A. I -- I wouldn't have any information to judge that, given the focus of my report was Pradaxa.

Q. Do you agree with me that it's a concern for warfarin parents if they're not in

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therapeutic range in terms of either much higher bleed risk or much higher stroke risk?

A. Yes.

Q. And even when warfarin patients are in range, they still have a meaningful bleed risk.

MR. MOSKOW: Objection to form.

A. That's my understanding of the data.

Q. Okay. And for that reason, for all those reasons, there was a desire in the medical community to have alternatives to warfarin; correct?

A. That's very much true.

Q. And Pradaxa was the first successful alternative to warfarin in 50 years; is that true?

A. So Coumadin was '54? Pradaxa was 2010? Yeah.

Q. Correct.

A. Yeah.

Q. And Pradaxa was viewed in the medical community as a substantial benefit in terms of a new form of anticoagulant treatment other than just warfarin; correct?

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MR. MOSKOW: Objection to form.

A. Yes, there was initial excitement.

Q. One of the reasons for that is the data showed that Pradaxa 150 was significantly better than warfarin at preventing strokes in systemic embolisms; correct?

MR. MOSKOW: Objection to form.

A. That's what's reported in the RE-LY publication and in the FDA reviewed sponsors label.

Q. You don't take issue with that being a fact, do you?

A. No, I don't.

Q. One of the reasons for excitement about Pradaxa being approved was that it had lower rates of life-threatening bleeds and lower rates of brain bleeds, intracranial hemorrhage; correct?

A. That's --

MR. MOSKOW: Objection to form.

A. Yes.

Q. Those are all wonderful things; right?

MR. MOSKOW: Objection to form.

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A. Yes, in the data set, yes.

Q. And you don't take issue with any of those facts, do you?

MR. MOSKOW: Objection to form.

A. No, I don't.

Q. Okay. So in that regard, do you review -- do you view Pradaxa as a meaningful advancement over warfarin --

MR. MOSKOW: Objection to form.

Q. -- in terms of statistically reducing stroke risk, statistically reducing the risk of life-threatening bleeds, and statistically reducing the rate of intracranial hemorrhage?

MR. MOSKOW: Objection to form.

A. For the average patient, yes.

Q. Now, the reason I -- I -- I went through that is it took Boehringer time to develop Pradaxa; correct?

A. That's my understanding from the documents.

Q. And it took -- and -- and -- and just focusing on Pradaxa, you understand that the data tells us there's a lot of money spent on trying to invent medicines that just don't end

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up working; right?

MR. MOSKOW: Objection to form.

A. I don't have any direct information about that.

Q. Well, you must -- you've quoted me a lot of pharma data. You must have seen pharma data on the amount of money that's invested and the amount of efforts that don't pan out before you actually discover a medicine that works. Right?

A. That's true.

Q. And I think the data I've seen, it's -- it's -- it's not one to one. Many more medicines fail than work; right?

MR. MOSKOW: Objection to form.

A. That's correct.

Q. And in this space specifically, did you know that there were other attempts to introduce alternatives to warfarin before Pradaxa that just didn't work?

A. I have read about that.

Q. It was -- I think the period of time, like the 50 years that passed between warfarin being invented and Pradaxa being invented, was

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not the scientific world being lazy and not looking at it. It was a hard thing to come up with an alternative; correct?

A. I think that's a valid interpretation.

Q. And with respect to Pradaxa, Boehringer could not be sure that Pradaxa would be this, you know, one-in-whatever medicine that actually works as opposed to one of the ones that failed until they saw the results of the RE-LY data; correct?

MS. PRESBY: Objection, form.

A. By definition, a development program's driven by the data.

Q. Right.

A. So that's true.

Q. Do you know when Pradaxa -- when -- when -- when the scientists at Boehringer first learned the results of the RE-LY data?

A. I don't know the exact date. I know it was sometime before submission of the NDA so it would have been sometime before 2010 but I don't remember exactly when the scientists saw -- because there was topline data, there

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were detailed data, so that was over a period of time.

Q. Are you aware that it was a year or two before the launch date?

A. That was my understanding. I mean, that's based upon what I read.

Q. And in the testimony you read, did you capture that sense of how amazed people were by the data, by how good it made Pradaxa look?

MR. MOSKOW: Objection to form.

A. Well, it's hard reading documents to sense amazement.

Q. Okay, fair enough.

Are you aware that the RE-LY study was designed only to show that Pradaxa was not inferior to warfarin?

A. Well, it was my understanding that there was a initial test for noninferiority but then a secondary test for superiority, which it then accomplished --

Q. And the --

A. -- for the 150 dose.

Q. Did you know that the trial design

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was a noninferiority trial?

A. Well, that's -- the primary end point was noninferiority, yes.

Q. Did you -- did you know everyone was, in fact, surprised that 150 was, in fact, superior?

MR. MOSKOW: Objection to form.

A. Yeah, I don't know what everybody thought. And there would be no way for me to know level of surprise in the company.

Q. Did you know the FDA was pleasantly stunned by the results and communicated that to Boehringer?

MR. MOSKOW: Objection to form.

A. I had access to the documents, and I think FDA was looking for treatments that went beyond the Coumadin paradigm, and I think they were encouraged.

Q. That's one of the reasons they had been such supporters of Pradaxa; right?

MR. MOSKOW: Objection to form.

A. That's my understanding.

Q. And, in fact, did you see the testimony from Dr. Reilly that, when they gave

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the results of the RE-LY study to the FDA, the FDA said this changes everything?

A. I've seen the quotes.

Q. Do you have any reason to take issue with that?

A. I would have no independent information to doubt that.

Q. From your understanding of what the RE-LY study shows about Pradaxa versus warfarin would you agree with that characterization, it changes everything --

MR. MOSKOW: Objection to form.

Q. -- in terms of the superiority on bleeds, on strokes, on life-threatening bleeds?

MR. MOSKOW: Objection to form.

Q. Would you agree with that?

A. If it -- meaning -- if -- if you mean -- and please clarify -- it changes everything because now we have a medicine that doesn't need monitoring, I disagree with that.

I think it was a incremental advancement. It certainly was superior to Coumadin and certainly was a therapeutic advancement over Coumadin, but I think the goal

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of having no one monitored might have been an overreach.

And I think some of what I have been talking about for labeling changes is to make what is a good product and a advance even better from a benefit/risk standpoint.

Q. So let me see if I understand what you just said.

You agree with me that from a medical standpoint, Pradaxa, even without monitoring, is a meaningful improvement over warfarin.

A. Yes.

Q. Do you know whether -- let's go to 92 in your report.

You say BI should have done one of three things regarding the reversal agent down at the bottom of the page in 252. "I believe BI should have done one, some, or all of the following."

Do you see where I'm reading?

A. Yes.

Q. And the first thing you say they should have done is they should have informed the FDA of the proof of reversal agent concept

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immediately.

Do you see that?

A. Yes.

Q. What is the proof of reversal agent concept?

A. Well, it was my understanding that the information that that initial work had been done and that there was a belief that creating a reversal agent was feasible, that information wasn't communicated to the FDA.

So as part of their NDA review, they did not know that there was the potential for a reversal agent to be developed at that time that they were reviewing the NDA.

Q. What's your understanding of the first time at which BI communicated to the FDA that there was a potential reversal agent?

A. My understanding was that it was after approval, but I don't have specifics.

Q. Do you rule out that they informed the FDA before approval that they were making efforts to develop a reversal agent?

A. I don't -- don't rule it out.

Q. Second thing you say is that they

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should have redoubled efforts in 2009 to bring Praxbind to market as soon as possible.

Do you see that?

A. Yes.

Q. Have you studied the efforts that Boehringer made in 2009 on Praxbind?

A. I -- I reviewed the document.

Q. Did Boehringer make efforts to develop Praxbind in 2009?

A. They appeared to make some efforts that then accelerated later on.

Q. You say a little later in here -- actually, maybe you say it a little earlier in here -- that -- it's on page 91 at paragraph 247, you say in 2014 there was a direction that the reversal agent was the highest priority project for the company.

Do you see where I'm reading?

A. Yes, I do.

Q. Are you telling me that that statement was not made before 2014?

A. I'm sorry, can you clarify which statement wasn't made?

Q. The one about the reversal agent

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program being the highest priority project for the company.

Do you know if it was the highest priority project for the company at any point before 2014?

A. The only documentation that I saw that it was the highest priority was in August -- was in 2014. So I didn't see that in anything stated that I read that that was the case in 2008 or 2009.

Q. Okay. Do you know that -- do you rule that out that that was the case before 2014?

A. I can only refer to the documents that I studied and so if there was a document that I didn't see then that -- that is possible.

Q. Go with me, if you would, to the third option you give, which is they should have delayed marketing of Pradaxa until Praxbind -- until it could be marketed with a reversal agent.

Do you see that?

A. Yes.

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Q. Is it honestly your opinion that, given the advancement that Pradaxa represented without a reversal agent over warfarin, they should have kept that advancement off the market until they had a reversal agent?

MR. MOSKOW: Objection to form.

Q. Is that your testimony?

A. I think -- yes, yes, it is, because the addition of a reversal agent has enhanced the benefit/risk. And it's enhanced it now, which means it would have enhanced it then.

Q. Okay. And I get your point, and I'll talk about it in a minute. But it would have been nice if it would be have been faster; right?

You made that point; right?

A. Correct.

Q. My question is this. Given where Pradaxa -- I'm sorry, given where the Praxbind development was in 2010, would it have been ethical for BI to keep Pradaxa off the market for four years and subject patients to only warfarin while it completed development of Praxbind?

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MR. MOSKOW: Objection to form.

A. Well, we have documented I'm not an ethicist.

Q. Okay. Let me ask the question differently. Would it have been the right thing in your view to do, consistent with patient safety, for Boehringer to say we don't have a reversal agent yet, let's keep this product off the market until we develop one and subject patients to a product that, among other things, cause -- results in more strokes, more major bleeds, more intracranial hemorrhage, more drug interactions, more food interactions, more monitoring?

MR. MOSKOW: Objection to form.

A. Well, I -- I think --

Q. Would that be appropriate?

A. I -- I think that my -- the way I wrote it was that when it was made a top priority in 2014, the amount of time between then and the time it was submitted and approved was a fairly short period of time.

Q. Wait a second.

A. And -- and if that emphasis had been

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placed back in 2008, it would have been available to be submitted to FDA at the same time as the NDA so there would have been no delay in the NDA because the BLA would have been developed because they were able to do it from 2014 to approval and that sort of intensity, if it had been done earlier, would have led to there not being a delay.

Q. Is it really your testimony that had they just applied that intensity in 2009, they could have gotten it approved within a year?

A. I'm saying that --

Q. Is that your testimony, sir?

A. No, that's not my -- that's not accurate.

Q. I'll ask a different question.

Are you aware that there were substantial efforts undertaken regarding the reversal agent in -- between 2019 [sic] and 2014 that allowed for that quick approval after 2014?

MR. MOSKOW: Objection to form.

A. I -- I -- I read about that in the documents. There -- there were -- the -- the

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fact that such amazing progress was made once the energy was focused on it, one cannot help but think that if that sort of energy had been placed earlier, it would have led to an earlier approval.

Q. How many -- how many scientists were focusing on the reversal agent in 2009?

A. I don't know.

Q. 2010?

A. Is part of your question is the number of scientists equal to the number of --

Q. Just asking how many scientists were working on the reversal agent in 2010.

A. I don't know.

Q. Do you know the number of scientists who were working on the reversal agent at any point in time?

A. No, I don't.

Q. Do you know the amount of money that Boehringer was spending researching the reversal agent at any specific point in time?

A. No, I don't.

Q. Do you know the amount of patients or animals that were being studied by Boehringer

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at any specific point in time?

A. No, I don't.

Q. How many animal studies were conducted on the reversal agent?

A. I don't know.

Q. When were they conducted?

A. I don't know.

Q. How many human studies were conducted?

A. I don't know.

Q. When were they conducted?

A. I don't know.

Q. Okay. How much engineering -- you -- you -- you talk in your report about there were mouse antibodies. I'm looking at page 90. There were mouse antibodies identified in 2002.

Do you see where I'm reading?

A. Yes.

Q. Is that accurate?

A. Based upon the documents I saw, yes.

Q. Are you sure it was mouse antibodies as opposed to rabbit antibodies?

A. I didn't see -- let's see. I didn't say what species.

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Q. First line of 246: "BI identified mouse antibodies" --

A. A mouse antibody.

Q. -- "in 2002."

A. My intent was to reflect what was in the documents.

Q. That's not my question.

Do you know if BI had mouse antibodies to dabigatran that it worked off of in 2002 or rabbit or any other species of animal?

A. I --

MR. MOSKOW: Objection to form.

A. I don't remember the details.

Q. Okay. In fact, if I tell you you're wrong about referencing mouse antibodies in 2002 do you have any reason to disagree with me?

MR. MOSKOW: Objection to form.

A. I -- no, I don't.

Q. Let me ask you some general questions. And we're late in the day. I'm going to read to you from a declaration I've seen in the AbbVie case where you worked on a

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biologic issue? Do you remember being asked about that earlier in the day?

A. Yes.

Q. Do you agree with me that developing an -- strike that.

Praxbind is a biologic product; right?

A. Yeah, BLA.

Q. But Praxbind itself is a biologic; right?

A. Yes.

Q. That means it's developed from -- I'm going to say this really poorly -- biological material like cells or something like that as opposed to a chemical; correct?

MR. MOSKOW: Objection to form.

A. Correct.

Q. Do you agree with me that developing an investigational biologic product is neither routine nor predictable?

A. I agree.

Q. Do you agree with me that biologic product development is a lengthy, complex product that remains unpredictable even for

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biologics where there's encouraging safety and efficacy data from Phase II clinical studies?

A. Yes.

Q. Do you agree with me that developing biologics can present unique patient recruitment challenges, ethical considerations such as risk to patients to the extent the regimen selected is unsafe and/or uneffective, limited supply of investigational biologic product, and significant time and resources required to conduct controlled clinical trials, each of which can hinder clinical trials in unexpected ways?

A. Yes.

Q. Do you agree that manufacturing monoclonal antibodies in particular is complex, expensive, and time-consuming?

A. Yes.

Q. Do you agree with me there are countless -- is -- is Praxbind a monoclonal antibody?

A. That was my understanding, but I -- I'm not -- I didn't spend a lot of time on the mechanism of action.

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Q. Do you agree with me that even after a company has conducted preliminary studies of a limited number of dosing regimens in Phase II trials, biologic and nonbiologic product development remains unpredictable and a substantial amount of additional work must be completed in order to determine what, if any, dosing regimen will be safe and effective?

MR. MOSKOW: Objection to form.

Q. Do you agree to that?

A. Yes.

Q. Do you agree that there are countless examples of failures in late-stage clinical trials for biologic and nonbiologic pharmaceutical products?

A. Yes, I -- I -- and how does that relate to what I said --

MR. MOSKOW: There's no question pending.

THE WITNESS: Okay.

Q. This -- this antibody, whether it was a mouse or a rabbit or whatever, that was, quote, on the shelf in 2002 that you -- that you talk about, was the -- whatever species it

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was that was, quote, on the shelf in 2002, was that the species of antibody that was ultimately used in Praxbind?

A. It's my understanding that it was then humanized so it was a humanized antibody used in Praxbind.

Q. Was it humanized from the same species that was on the shelf, or did they have to look at other species?

A. I -- I don't remember those details.

Q. Do you know that, in fact, they looked at multiple species before being able to settle on the right species?

A. That would sound legitimate.

Q. Do you know whether that's true in this instance or not?

A. I do not know.

Q. You suggest in your report that nothing was done before 2008.

Do you know if there were other efforts other than use of an antibody to develop a reversal agent?

A. Can you rephrase that first part? Because I -- you know, my statements in my

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report were based upon what I read and the emails so, you know, I was reporting what I had --

Q. Sure.

A. -- seen.

Q. Let me ask you, were there efforts other than through use of the antibody to develop a reversal agent before launch?

A. I don't remember details, but that's -- that sounds right.

Q. Going back into the early 2000s; correct?

MR. MOSKOW: Objection to form.

A. That's -- that certainly is consistent with some of the materials I read.

Q. And this specific effort regarding this -- use of this antibody, did you know what purpose the antibody was created for?

A. You mean as -- as a reversal agent? Is that what you're saying? Or why it was created originally?

Q. Yeah, back in 2002.

A. No, I don't.

Q. Do you know that it involved a

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substantial scientific insight that a Boehringer scientist had going to a scientific conference to think that you could use an antibody like this as a reversal agent?

A. I remember reading something, something about that.

Q. Okay. Do you have any reason to take issue with that proposition?

A. No, I don't.

Q. For example, are you aware of any instance in the history of science where a company has used an antibody as a basis for reversing the effects of their medicine in the way Boehringer did with Praxbind?

MR. MOSKOW: Objection to form.

A. There are some -- some -- I know of some examples, and I think they're still proprietary and confidential, from my time at FDA.

Q. Do you know of any public examples where a company has been able to develop a product using an antibody to reverse potentially harmful effects of their medicine other than Boehringer with Praxbind?

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A. No, I don't.

Q. The ones you mentioned that are proprietary and confidential, I take it those have never been approved.

MR. MOSKOW: Objection to form.

A. That's correct.

Q. And to this day, are you aware -- are you aware of how quickly Praxbind works?

A. I don't have any direct experience on how quickly it works. I would refer to the sponsor's label.

Q. Are you aware that it works in minutes?

A. That sounds right.

Q. And are you aware of any product that reverses warfarin that fast?

MR. MOSKOW: Objection to form.

A. As we discussed this morning, the literature on Vitamin K and FFP quote longer time frames than that.

Q. So the answer is no, you don't know of any product that --

A. I don't know of any product that does it quicker.

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Q. Is there any reversal agent at all for the other novel oral anticoagulants?

A. Not that I'm aware of.

Q. Are you aware that there have been efforts to develop reversal agents for those novel oral anticoagulants?

A. I'm not aware of any specific efforts, but --

Q. But whatever efforts there have been have not succeeded to date.

MR. MOSKOW: Objection to form.

A. Yes, those -- that -- those have not led to an FDA approval as of today.

Q. Should those products be kept off the market absent a reversal agent?

A. Well, my -- my report focused on Pradaxa so it would be outside the scope of my report to comment if other products should or should not be kept on the U.S. market.

Q. I'm asking based on your reasoning about Pradaxa and your knowledge about oral anticoagulants, should the other oral anticoagulants be kept off the market until they develop a reversal agent?

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MR. MOSKOW: Objection to form, asked and answered.

A. When we were going over the various recommendations I had, it was that, you know, an acceleration of the Praxbind development program to correlate with introduction of the Pradaxa NDA, not at the emphasis of delaying it, because nothing I said in my testimony for the patent case contradicts the belief that since things are expensive, then additional resources do accelerate the process.

And I think it's quite clear in industry that if you do put additional resources to a project, that often speeds it up. I mean, that's sort of the mainstay of, you know, industry thinking in the space. How can we accelerate the development process? And it's often with dollars and people.

And so if there was already maximal effort, then what good would it have done to say that this is now our top priority if it had always been their top priority? So that was my reasoning process.

Q. Okay, move to strike and note that we

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have had another page-long answer that's --

MS. PRESBY: I'm going to object to that characterization.

Q. -- that's arguing with -- with several lines of questions back. My question is --

MS. PRESBY: I object to the characterization of the length of the answer, by the way. No need to exaggerate.

Q. My question was simply, sir, in evaluating whether Boehringer acted reasonably, either in the timing of the reversal agent development or in the fact that there was a period of time when Pradaxa was on the market with no reversal agent, have you done -- have you looked to the actions of other reasonable pharmaceutical companies that have also brought novel oral anticoagulants to market?

MR. MOSKOW: Objection to form.

A. That was not the scope of my report. My focus was on Pradaxa and what BI did or didn't do.

Q. So is the answer to my question no,

you haven't looked at the actions of the other companies?

A. I haven't looked at the actions of those other companies because that has no bearing on FDA regulation of safety and efficacy. It's not comparative.

Q. Are you offering opinions based on what a reasonable company would do?

A. Yes, I am, what this reasonable company could do.

Q. You said a moment ago that -- you said a moment ago that the document you cite, for the highest priority document you cite on page 91, that that was the highest priority project for the company.

Do you see that?

A. Yes.

Q. And you reference a document that ends with the Bates number 404; correct?

A. Yes.

Q. And you said just now in your answer, why would you need to say it was the highest priority if it already was the highest priority; right?

A. If -- yes, that's correct.

Q. Did you read that full document?

A. Yes, I did read the document.

Q. Okay. Did you know that you left out really important language in that quote?

A. Can you clarify? I -- I feel -- I feel I included the language of getting the point across that -- that perhaps prior to that, 100, you know, maximal effort was not being used.

Q. Okay.

A. And once maximal effort was used, it led to a -- a successful product that was approved.

Q. Do you remember the language you omitted from your quote?

A. I don't remember what I omitted. That was how many months ago?

Q. Do you -- do -- is it your understanding that you included the important language in the quote?

A. My intent was to include the important language in the quote.

Q. I'm going to read you the language

you omitted.

MR. MOSKOW: What page?

MR. SCHMIDT: It's page ending in the Bates label 406. Do you have that there, Neal?

MR. MOSKOW: Uh-huh.

MR. SCHMIDT: I'm sorry, I don't have a copy of this so I'm going to read it and Mr. Moskow can tell me if I've misread it.

MR. MOSKOW: Is it all right if I show it to the witness on the screen?

MR. SCHMIDT: Sure.

BY MR. SCHMIDT:

Q. Let's go to the start of this document. Do you see where Mr. Moskow has put in front of you a document that the first Bates number's the same one you cite, 404?

A. Yes.

Q. And this is, in fact, as you say -- well, do you -- do you know -- it says at the top Final Minutes, IDC2, 2014.

Do you see that?

A. Yes, I do.

Q. And if you scroll down to page 406, the last page of the document, it has decisions and conclusions.

Do you see that?

A. Yes.

Q. One of the decisions and conclusions, the third one, specifically contains that language. What -- what is -- I can never say this. What is idarucizumab?

A. Are you asking me a question?

Q. Yes. Do you know what idarucizumab is?

A. Well, that's the -- the monoclonal antibody.

Q. Okay. That's the -- that's Praxbind?

A. That's Praxbind. And since it's a -mab, M-A-B, it's a monoclonal antibody.

Q. And it has that language you quote about Praxbind being the highest priority project for the company.

Do you see that?

A. Yes, I do.

Q. Let's look at the language you omitted. The language you omitted says the IDC

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confirmed that it was the highest priority project for the company; correct?
A. Yes.
Q. Doesn't that indicate, if you confirm something, that it was already the case?
A. Not if you read the second part of the sentence where it says "to ensure sufficient resources," because that means that it may or may not have had sufficient resources and planned upcoming submission.
So, you know, that infers that, yes, they're confirming that now it's the highest priority, but that doesn't mean that it was the highest priority before and they want to ensure that it has sufficient resources.
Q. Do you know one way or the other whether it was before?
A. I -- I would have thought they would have worded it "to continue sufficient resources" if that was the case, so the wording is vague.
Q. Do you know one way or the other whether it was the highest priority before?
A. It was my impression that it was now

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the highest priority as of 2014.
Q. Do you -- do you know?
A. I know -- all I know is what I've read in the documents.
Q. Okay. Have you seen earlier documents where they talk about it being a high priority or a company priority or the funding they're devoting to it?
A. No, I have not. This is the first time I saw it was the highest priority, which is why I made note of it and included the quote.
THE REPORTER: Let's take a break soon.
MR. SCHMIDT: We can do that now.
THE VIDEOGRAPHER: We're off the record at 5:35.
(Recess taken.)
THE VIDEOGRAPHER: We are back on the record at 5:51.
MR. MOSKOW: I just wanted to say quickly, counsel continue to work together as best we're able to do. We've have agreed to continue the

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deposition beyond the 7 hours under CMO-18 protocol for a reasonable period to allow counsel to complete his questioning but I would just note that Dr. Harvey is recovering from an illness, and the day has been long, and he's indicated he may need more frequent breaks.
THE WITNESS: Thank you.
MR. SCHMIDT: In our view, the extra time is appropriate, but I also am grateful for your professionalism in offering it without -- with great graciousness, as is customary from you.
As to how you're doing health-wise, doctor, candidly, I'd forgotten that. Mr. Moskow several weeks ago mentioned to us that you had a health concern and we had to move the deposition. Obviously, we immediately agreed to it. I hadn't thought of it since in terms of if there was any ongoing issue. If you need a break at any time, let me know immediately, for health reasons. I will

HARVEY
squawk if you break for nonhealth reasons, but I think I'm within my rights to do that. But obviously, if you have a health concern, please let me know.
THE WITNESS: Okay.
MR. SCHMIDT: And we want to be accommodating on that.
THE WITNESS: Okay.
BY MR. SCHMIDT:
Q. I don't want to make it sound like one or two, but I have a few more topics to cover that I think will be discrete and individually reasonably quick, and I want to walk through them.
On page 24 of your report carrying over to page 25, you state that the current label does not adequately warn or quantify the bleeding risk in specific subpopulations.
Do you see that?
A. Yes.
Q. And you identify age greater than 80, mild and moderate renal impairment, weight less than 50 kilograms, and concomitant medications,

HARVEY

e.g., SSRIs.

Do you see that?

A. Yes.

Q. What should the label say about SSRIs?

A. Could you give me a context of what you're -- what you're saying or what you're asking?

Q. You say the label does not adequately warn of specific issues, and one of them is SSRIs.

What should the label say about SSRIs?

A. So you had me looking at table 10?

Q. No, no, no. Look at the paragraph 76.

A. Okay.

Q. "As noted below, the current label does not adequately warn of or quantify the bleeding risk in specific populations." And then it identifies age, renal impairment, weight, concomitant medications.

Do you see that?

A. Yes.

HARVEY

Q. And the example given of concomitant medications is SSRIs.

Do you see that?

A. Yes, I do.

Q. Have you seen any studies that show the effect of SSRI use on Pradaxa patients?

A. I am looking to see where I got that from. So there has been a concern in elderly patients that certain -- use of certain medications increased their chances of falls. FDA's been concerned about that, more with the atypical antipsychotics, but also with other centrally acting medications.

So I think I had used that as an example just that you don't have to have a strict traditional drug/drug interaction, you know, like the verapamil and ketoconazole and quinidine to have a concern about drug/drug interactions. And that's information I've taken from my days at FDA.

Q. What -- what are --

A. I don't have a citation for that.

Q. What are the -- what's the effect of using an SSRI in a Pradaxa patient?

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A. I think it was more directly the -- it's an SSRI on an elderly patient who may fall. And then, you know, it would increase their risk of bleeding, not directly to Pradaxa, but to them falling and any sort of anticoagulation.

So I didn't intend that to be Pradaxa-specific, and it could have -- could have had some additional description there to illustrate the point.

Q. Do the SSRI labels warn of risk of falls in elderly patients?

A. I have to go back and see what has been put in the various labels. There's been discussions about that. I need to follow up on that.

Q. Okay. Do you know of any SSRI labels that warn about use of SSRIs with anticoagulants?

A. I remember that there's a section there. I know the labels have been updated over time.

Q. To warn of use of SSRIs with anticoagulants?

HARVEY

A. I would have to look at those labels.

Q. Does any other -- I take it the concern you raise would apply, the SSRI concern you raise would apply with all anticoagulants; right?

A. That's my understanding.

Q. Do you know if any anticoagulant warns -- has a warning regarding SSRIs?

A. I didn't do that review.

Q. Okay. So you don't know?

A. I don't know.

Q. Weight, and mild and moderate renal impairment. Do you see those categories as categories you identify that should have warnings?

A. Yes, I do.

Q. Does the label currently have any information on how either weight or level of renal impairment impacts major bleeding risk relative to warfarin?

MR. MOSKOW: Objection to form.

A. There is some information in the label, but I -- you know, my statement was that there needed to be more information.

HARVEY

Q. And what is the more beyond what exists that should be added?

A. I outline --

Q. With respect to mild and moderate renal impairment and weight less than 50 kilograms.

A. Well, we -- we talked about that before, that weight less than 50 kilograms, there's an increased risk of having a dose result in high plasma levels, which increase -- and higher risk of -- of bleeding events.

Q. What do you base that on?

A. The articles that we have been talking about all day.

Q. I didn't see any articles that talked about an increased risk of bleeding in patients --

A. Under 50 kilograms?

Q. Yes.

A. Well, it's in the documents.

MR. SCHMIDT: Well, let me show you a document. Why don't we go ahead and mark the 2015 label as -- exhibit what? 22?

HARVEY

(Harvey Exhibit No. 22 was marked for identification.)

BY MR. SCHMIDT:

Q. And look with me, if you would, at figure 1 in the 2015 label, Exhibit 22.

A. I'm sorry, which page?

Q. Figure 1. It's about six pages in. I'm going to give you a second version. Do you see on -- do you see figure 1 in the 2015 label?

A. Yes, I do.

Q. And do you see that it reports bleed data by different baseline characteristics?

A. Yes.

Q. Comparing Pradaxa to warfarin?

A. Yes.

Q. Specifically, it reports data on the effect of Pradaxa on patients above 60 kilograms versus below.

Do you see that?

A. Yes.

Q. And there's no difference between those two groups?

A. And we look at the end and there's

HARVEY

only, what, 43 under 60 kilograms in the Pradaxa group, and only 50 patients in the warfarin group, so it's sort of underpowered.

Q. Am I correct that there's no difference between the two? They have almost identical point estimates?

MR. MOSKOW: Objection to form.

Q. .96 and .97?

A. And I would say that the -- the N, the numbers are small.

Q. Before you get to the speech, could you tell me if what I said is right, that they're almost identical, over 60 kilograms and under 60 kilograms?

A. The -- in this -- in this representation, they are similar.

Q. Are you aware of any contrary data?

A. I remember seeing some document that discussed that patients under 50 kilograms were at increased risk of bleeding.

Q. Can you point me to those documents?

A. No, I can't. It's here somewhere.

Q. If you look a little further down, it gives data based on different levels of renal

HARVEY

function.

Do you see that?

A. Yes.

Q. And if you get below 30, there's quite a dramatic difference between Pradaxa 150 and warfarin.

Do you see that?

A. Yes.

Q. And that's why there's a lower dose recommended for patients below 30; correct?

A. Yes.

Q. Once you're above 30, though, again, the estimates are -- are very similar. 1.02, .92, .90 are the different ranges above 30; correct?

A. That's what it says.

Q. Have you seen any contrary data?

A. Well, I went to the core data sheet on page 36. They talk about special populations and renal impairment.

And let me note that on figure 1 there were only three patients on Pradaxa with a creatinine clearance less than 30.

And if you see, the size of the

HARVEY

square correlates with the number of patients and so when you see a teeny tiny square, it's because you don't have a very large N.

Q. Sir, can you answer my question now? Have you seen any contrary data in terms of bleed rates at patients who have mild or moderate renal impairment?

A. In some of the documents that I've -- I've read.

Q. Can you point me to any specific ones?

A. Do you want me to take the time to find them?

Q. Can you do it without going through all the documents?

A. I guess I'm confused since, you know, there is information in the label about renal impairment. So I understand that figure 1 is figure 1, but I'm trying to reconcile that with all the other information I've seen.

Q. Have you seen any data contrary to the data in figure 1 suggesting that there are notably higher bleed rates in patients who have moderate or mild renal impairment versus

HARVEY

warfarin, or versus normal renal impairment in Pradaxa patients?

A. Yes, I have.

Q. But you can't point me to that right now?

A. I can't point you to that reference.

MR. SCHMIDT: Let me mark another exhibit. Let's mark the launch label. That will be Exhibit 23.

(Harvey Exhibit No. 23 was marked for identification.)

BY MR. SCHMIDT:

Q. This is the label from when Pradaxa first came on the market, correct, Exhibit 23?

A. Yes.

Q. Correct? This is the label from when Pradaxa first came on the market?

A. Yes.

Q. And you understand from the time Pradaxa has first come on the market that the label has warned of the risk of bleeding for older patients?

A. Yes.

Q. For example, under section 6.1 --

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A. Okay, I'm there.

Q. -- under the table 2 there's a reference to the risk of major bleeds being similar, with the exception of age, where there was a trend towards a higher risk of bleeding.

Do you see that?

A. Yes.

Q. And if you continue on the next page in section 8.5, Geriatric Use, it says the risk of stroke and bleeding increases with age.

Do you see that?

A. Yes.

MR. MOSKOW: Objection to form.

A. Yes.

Q. And then there's a medication guide attached to the Pradaxa label; correct?

A. Yes.

Q. And the medication guide says you may have a higher risk of bleeding if you take Pradaxa and are over 75 years old; correct?

A. Yes.

Q. Now, a few questions about this. Do you know why -- you talk in your report on page 25 about the risk of bleeding above the age of

HARVEY

80.

A. Yes.

Q. Do you know why the age 75 was used in the Pradaxa label?

A. Not specifically. I mean, and that was -- I -- I would assume that it's related to the RE-LY trial data.

Q. And specifically, do you know whether the age of 75 was a prespecified end point in the RE-LY study?

A. I don't remember that offhand.

Q. Do you know whether the age of 80 was a prespecified end point in the RE-LY study?

A. Prespecified end point or inclusion/exclusion?

Q. Prespecified end point.

A. That -- that, I don't remember.

Q. Does that have any implications for labeling language?

MR. MOSKOW: Objection to form.

A. Well, if --

MR. MOSKOW: You can answer even when he's not listening.

A. You know, if -- if you're conducting

HARVEY

a clinical trial and you don't have adequate number of patients in those various age groups it's very difficult to make recommendations about those age groups if you haven't adequately studied them.

Q. Do you know if there was adequate data on patients 80 and above to justify a warning about patients 80 above as opposed to 75 and above?

A. I don't know the details of that data, but the FDA criteria for warning is not the same as the FDA criteria for an efficacy claim; and therefore, the lack of data doesn't necessarily imply that you can't make a warning of a population.

Q. And so if you come back to my question, do you know if there was enough data to justify a warning for patients 80 and above in the RE-LY study as opposed to the --

MR. MOSKOW: Objection.

Q. -- the warning that was given for patients 75 and above?

A. I don't remember the details of 75 versus 80. I mean, they're both elderly

HARVEY

population; they're both Medicare population. I -- I don't know why that distinction was drawn. And practically, you know, the more conservative approach would be to use the 75 age cutoff.

Q. Conservative in a good way?

A. Conservative in a good way.

Q. Okay. So you don't take issue with using a 75 cutoff versus an 80 cutoff?

A. No, I don't.

Q. And you do take issue with one thing that I want to ask you about. On page 26, you say -- you go over that language you and I just talked about and you say to the extent that the label references a trend toward a higher incidence of major bleeding in patients 75 years old and older in section 6.1, this statement is immediately contradicted in label section 8.5, Geriatric Use.

Do you see that?

A. Yes, I do.

Q. So let's look at the language again one more time that you're talking about. Let's look at the 6.1 language in Exhibit 23 under

HARVEY

table 2. It says: "The risk of major bleeds was similar with Pradaxa 150 milligrams than warfarin with the exception of age, where there was a trend towards a higher incidence of major bleeding on Pradaxa for patients 75 years or older."

Do you see that?

A. Yes, I do.

Q. As far as you know, is that factually accurate, based on the data as it existed then?

A. Yes, that's my understanding.

Q. We then go to the statement you say is contradictory, section 8.5. The first sentence gives data on how many patients in RE-LY were in different age groups.

Do you see that?

A. Which heading?

Q. Under Geriatric Use, 8.5.

A. Yes.

Q. Where it talks about 82 percent of patients being over 65 and 40 percent being over 75.

A. Correct.

Q. Is that statement accurate as best

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you know?

A. Yes.

Q. It then says: "The risk of stroke and bleeding increases with age."

Is that a true statement?

A. Yes.

Q. "But the risk/benefit profile is favorable in all age groups."

Is that a true statement?

A. It depends on how much the stroke and the risk of stroke and bleeding increases with age. It depends on how much it increases because if it increases to a great degree, then it's no longer a favorable benefit/risk profile. And the extent of that increase isn't fully characterized.

Q. Let's take an age group 90 and above. If there were data showing that the risk/benefit profile was not favorable for patients 90 and above, should be contraindicated in those patients; right?

A. Or there should be a warning that it should not be used.

Q. Have you seen data that leads you to

HARVEY

believe that the risk/benefit profile is unfavorable for Pradaxa 150 in any age group?

A. My concern is that there isn't adequate data, let's say, for 90 and above in order to assure that that still has a favorable benefit/risk profile --

Q. Okay.

A. -- given that we know that bleeding risk increases with age.

Q. Come back to my question, please.

Have you seen data that indicates to you that any specific age group, Pradaxa has as unfavorable benefit/risk profile?

A. No, I've not seen clinical data that shows that.

Q. Look with me at page 40 of your report. On page 40 of your report in paragraph 116 you cite a document saying that the net clinical benefit in subjects over 80 years is marginally in favor of warfarin.

Do you see that?

A. Yes.

Q. Do you know how net clinical benefit was calculated in that -- as used in that

HARVEY

statement?

A. No, I don't.

Q. Do you know generally how net clinical benefit's calculated?

A. I don't -- I don't have the details right here.

Q. Do you -- do you know that net clinical benefit calculations of this type involve assigning a specified weight to strokes and a specified weight to go bleeds and then running a formula?

A. I know that the -- the folks in drug safety do the number of patients needed to treat versus the number of patients needed to harm and come up with it that way.

Q. Do you understand this to be a drug safety calculation as opposed to a medicine calculation?

MR. MOSKOW: Objection to form.

A. I don't understand the difference.

Q. You understand that Boehringer has a drug safety department; right?

A. Yes.

Q. And they're the department that's

HARVEY

responsible for something called pharmacovigilance; right?

A. Correct.

Q. That involves monitoring information that's generated in the real world from the drug; right?

MR. MOSKOW: Objection to form.

A. Yes.

Q. Including case report information where people call up and report events to the company; is that right?

A. Correct.

Q. Are you aware of -- and -- and -- and companies like Boehringer have an obligation under FDA rules to submit that data or certain forms of that data that they get to the FDA; right?

A. Correct.

Q. They have an obligation to submit certain case reports; correct?

A. Yes.

Q. Then they have the obligation to do periodic filings with the FDA on different safety issues.

HARVEY

A. That's right.

Q. And those filings are called PSURs or PSURs; right?

A. Correct.

Q. And you've seen that Boehringer made those filings; right?

A. Correct.

Q. Both individual case reports and PSURs or PSURs; correct?

A. That -- that's not been an issue in my report that reports were not filed.

Q. And that's -- that's what I wanted to ask you. Did you see any -- any pharmacovigilance data that Boehringer was required to submit that it did not submit?

A. That would -- I did not find that in my review.

Q. Okay. So let's go back to this example, this net clinical benefit statement.

Do you know the specific formula that was used to make that net clinical benefit calculation?

A. No, I don't.

Q. Do you know if you agree with the

HARVEY

formula in terms of the weighting of strokes and bleeds or not?

MR. MOSKOW: Objection to form.

A. Yeah, that's unknown. I don't know.

Q. Okay. Let's look -- do you know what else that document that you cite there says about how Pradaxa performs relative to warfarin in patients 80 and above?

A. No, I don't.

Q. Do you know if -- do you know if Boehringer ultimately had the view that Pradaxa was better than warfarin or was not better than warfarin for patients 80 and above?

MR. MOSKOW: Objection to form.

A. Can you --

Q. It was an inartful question.

Do you know if Boehringer's ultimate opinion or the -- the ultimate opinion of the scientists working at Boehringer was that Pradaxa was or was not better than warfarin for patients 80 and above?

MR. MOSKOW: Objection to form.

A. I don't know what the ultimate opinion was, I just know what was cited in that

HARVEY

document, that in that specific case, they felt that it was only marginally -- you know, warfarin was marginally better.

Q. Do you know what the ultimate opinion expressed in that document was as to whether warfarin or Pradaxa was better for patients 80 and above?

A. I --

MR. MOSKOW: Objection to form.

A. I'm sure that the documents said that Pradaxa was better.

Q. Do you recall that? Did you read the full document to see that?

A. I -- I -- I reviewed the document. I didn't study that in depth. I looked at the pertinent sections of the document.

(Harvey Exhibit No. 24 was marked for identification.)

BY MR. SCHMIDT:

Q. I'm going to pass you a document that I've marked as Exhibit 24. You'll see that this is the document that you cite that we have been discussing in your report. Is that correct?

HARVEY

A. It's --

MR. MOSKOW: It's an excerpt in the document.

A. It's an excerpt, yes.

Q. If you look at the third page of this excerpt, you will see a table 46.13 with a net benefit -- net clinical benefit calculation, and below that is the language that you quote about net clinical benefit.

Do you see that?

A. Yes.

Q. Did you read the full page here when you cited this document?

A. Let me look. Yes, I did read that.

Q. Okay. So you saw that they went on to conclude that dabigatran has favorable rates of intracranial hemorrhage in subjects 80 and above; correct?

A. Yes.

Q. Less than a quarter of the rates for warfarin; correct?

MR. MOSKOW: Objection to form.

A. That's how it's described here.

Q. As well as favorable rates of stroke;

HARVEY

correct?

A. The stroke rates, yes.

Q. They are actually 35 percent lower in patients 80 and above; correct?

MR. MOSKOW: Objection to form.

A. Yes.

Q. And they ultimately conclude subjects at least 80 years of age have a high risk of stroke or intracranial hemorrhage.

Do you see that?

A. Yes.

Q. Do you agree with that?

A. Well, but then there's a section you left out where the benefit is driven primarily by major bleeding where the excess bleeding with Pradaxa is primarily GI bleeding.

Q. Move to strike as nonresponsive. Do you agree with the statement that subjects at least 80 years of age have a high risk of stroke or ICH, intracranial hemorrhage?

Is that a true statement?

A. Yes, it's a true statement.

Q. They go on to say: "These subjects have a clear benefit with dabigatran compared

HARVEY

to warfarin in reduction of the risk of stroke and of intracranial hemorrhage."

Did I read that correctly?

A. Yes, you did.

Q. Okay. Do you -- do you agree that that's a true statement based on the data you've seen?

A. Yes, given the context of that sentence, that's a true statement.

Q. And they then reach their conclusion, and that's what I want to ask you if you agree with.

"These advantages in stroke, SEE prevention, and rates of intracranial hemorrhage counterbalance the excess extracranial bleeding."

Did I read that correctly?

A. Which paragraph was that? I'm sorry.

Q. It's the last sentence in the paragraph we were just looking at.

A. Oh, okay. You were reading up there and now we're down here.

Q. No, it's the same paragraph I was reading from.

HARVEY

A. Okay, yes, I see that.

Q. Do you agree with that statement, that the advantages that Pradaxa 150 has over warfarin in patients 80 and above in stroke and SEE prevention and rates of brain bleeds counterbalance the excess bleeding outside the brain that you see with Pradaxa 150 in patients 80 and above?

MR. MOSKOW: Objection to form.

A. Yeah, I don't agree with that just because that's a value judgment about the seriousness of GI bleeds versus intracranial bleeds.

Q. Okay. Do you disagree with it or do you just not have a view one way or the other, as a general proposition?

A. I think it's vague enough that I would have to not have a view.

Q. Okay. You don't agree or disagree?

A. It's open to interpretation, and you could either agree or disagree depending on how you interpret it, so I have no opinion.

Q. Okay. You talked at various points in your report about assays; correct?

HARVEY

A. Yes.

Q. And I want to focus -- we've talked a little bit about that, but I want to focus on one specific statement you make that struck me as quite strong. And that's on page 26 in your report. I may have asked you this, and I apologize.

Have you ever administered the APT -- APT -- have you ever administered the APTT test?

MR. MOSKOW: Objection to form.

You can answer.

A. I have ordered, you know, a PT -- PTT -- APTT INR many times during internship, residency, fellowship, and my hospitalist work.

Q. There's data that exists regarding how the APTT test performs with Pradaxa. Are you aware of that?

A. Yes.

Q. Have you made a point of studying that data?

A. I've looked at the various documents and read about, you know, the differences in reagents and different values.

HARVEY

Q. And that's what I want to ask you. I have heard it said that the APTT test is more reliable -- and I think you alluded to this earlier -- is more reliable at certain plasma concentration ranges than at others.

Have you heard that?

A. Well, the fact that it's -- if it's off the scale, so when you have a very, very high APTT, it's more than likely going to be off the scale regardless of the reagent and therefore, that is something that's reproducible across the various assays, and that would correlate with a high drug level.

Q. Let me ask you this. We have been talking throughout the day about different plasma concentrations in terms of nanograms per milliliter; correct?

A. Correct.

Q. And we've talked about anything from 0 to 100 to 200 or higher than 200, 300 and above; correct?

A. Right.

Q. Is -- is there a particular part of the range where you believe that the APTT test

HARVEY

is reasonably accurate?

MR. MOSKOW: Objection to form.

A. I believe, and it would be inferred, not directly measured, that to get an APTT greater than 200 or off the scale, you would be up at the higher concentrations of drug in -- in the serum.

Q. I think you're answering a different question, I think, because my question's vague. Let me take a measure. You've used the measure of 150 nanograms per milliliter.

Do you remember that?

A. Yes.

Q. Okay. Can the APTT -- the APTT measures it in a different way. It measures it in seconds; right?

A. Correct.

Q. But you're aware that the Pradaxa label gives data on the APTT measurement that corresponds to the 10th percentile of plasma concentration exposure from RE-LY and the 90th percentile; correct?

MR. MOSKOW: Objection to form.

Q. Are you aware of that?

HARVEY

A. Yes.

Q. Here's -- here's my question. If you have a plasma concentration of 150 or above, can the APTT reliably tell you that fact if you're above 150?

MR. MOSKOW: Objection to form.

A. If the APTT test came back off the scale, you'd know you would have a high level, but I don't know how much higher and it would probably be significantly higher than just 150.

Q. Okay. Do you know where -- at what level you can reliably tell that, in your opinion, you have too much anticoagulation from the APTT?

A. Well, it's -- it's -- you know, if it's off the scale, then you obviously have too much.

Q. What's off the scale?

A. That's when the reading is -- when they stop giving you seconds, it's just the maximum reading. And you know that's too much.

And then if it's -- you know, I've seen things anywhere from two to three times the upper limit of normal as being too much.

HARVEY

So it's a relatively crude measure, but if it comes back at a very high level then you know that you've got a very high amount of anticoagulation on board.

Q. From the time of -- of -- of launch -- and if you want to look at the launch label, it's Exhibit 23. If you look at section 12.2, there's a paragraph, the first paragraph under section 12.2, the third sentence -- I'm sorry, the second sentence says in -- I'm sorry, the -- the third sentence says: "In the RE-LY trial, the median," and then it says "10th to 90th trial, trough APTT in patients receiving the 150-milligram dose, was 52 with the 10th percentile 40 and the 90th percentile 76 seconds."

Do you see that?

A. Yes.

Q. Do you know if you get a measurement of 76 seconds on the APTT if that's reliable?

MR. MOSKOW: Objection to form.

A. It's my understanding that the APTT test has more utility at that high end to -- to eliminate individuals who are getting too high

HARVEY

a dose and that the precision closer to that range of 50 to 150 hasn't -- hasn't shown as much utility.

Q. So if I understand what you said just right, the APTT test is good at telling you if you're -- if you have a high coagulation, it's less precise at telling you if you have a low one --

A. In --

Q. -- or the middle of the range?

A. In theory, you should be able to tell when you're too low because you haven't bumped it at all. And I would need to see the data on that, so -- but a generalization would be, you know, extremely high or extremely low, there's utility.

Q. And then it goes on to report ECT data, the median with the ECT and the 10th and 90th percentile. Do you see that?

A. Yes.

Q. And the ECT is the test you said that you looked on the Internet and you saw was widely available, correct, in the United States?

HARVEY

A. I think there was some confusion about that based upon our discussion.

Q. Is the ECT widely available in the United States?

A. The ECT is one that's available -- now you're getting me all confused here. People do have access to it, but, you know, widely available, there's some question to whether, you know, I had the documentation on the web to state that.

Q. Okay. Going back to page 26 of your report.

MR. MOSKOW: The report?

MR. SCHMIDT: Yes, the report.

Q. If you look at page 26, which I think you have open there, you reference the fact that -- you -- you talk about the APTT test and you say: "Finally, because APTT reagents vary in sensitivity, recommending that physicians use APTT to assess a Pradaxa patient's anticoagulation status is reckless without specifying which reagent should be used for that assessment."

Did I read that correctly?

HARVEY

A. Yes.

Q. And that was the strong language about reckless that I was referring to. Here's my question. Which APTT reagents are available in the United States?

A. I don't know the specific reagents. I -- I could look at it and, you know, I know there are -- there are various ways to conduct the test, but I don't remember exactly which -- which buffers and which -- what are the specifications.

And when a physician orders it, they check the box, they draw the blood, they send it off and they give you a reference range. So, you know, the actual reagents that are used aren't something that's -- that's remembered but you know what the range is for your institution and what that number needs. The only problem is when you're trying to compare from one institution to another.

Q. Do you know if there's more than one reagent commonly used in the United States?

A. I don't -- I don't know who uses what reagent and whether one's more common or -- or

HARVEY

not.

Q. For example, if I told you one reagent was used by 95 percent of facilities in the United States, would you have any reason to disagree?

A. No, I --

MR. MOSKOW: Objection to form.

A. No, I wouldn't.

Q. Do you know if there is any difference between the reagent that's most commonly used in the United States and the one that was used in RE-LY and reported in the label?

MR. MOSKOW: Objection to form.

A. No, I don't.

Q. Do you agree with me that APTT provides an approximation of anticoagulation activity in Pradaxa applicant?

A. It provides an approximation when looking at the entire range, and it's better at that high range.

Q. On page 36 you quote an email exchange between Dr. Clemens and Mr. Kannan.

A. Which page?

HARVEY

Q. Page 36, paragraph 106. This is an email chain about a bedside device.

A. Okay.

Q. Do you understand that quote?

A. "Are you asking for a bedside device"?

Q. Yeah. Do you see the quote, the communication between Dr. Clemens and Mr. Kannan?

A. Starting with which word?

Q. "Are you asking for a bedside device."

A. Yes, I do.

Q. Mr. Kannan is in marketing; correct?

A. That's my understanding.

Q. And he's not a scientist?

A. I don't know if he's a scientist or not but his title is team leader, marketing.

Q. Dr. Clemens is not in marketing. He's in the science area; correct?

A. Yeah, he's in the therapeutic area.

Q. He is, in fact, a scientist; correct?

A. He's a doctor.

Q. Do you know that he's also a

HARVEY

scientist?
A. How would you define scientist?
Q. Someone who studies science.
A. Then he is a scientist.
Q. Okay. And in this email, who is it that refers to the no monitoring idea/claim?
MR. MOSKOW: Objection to form.
A. The team leader.
Q. Dr. Clemens; right?
A. Yeah.
Q. And Dr. Clemens, I take it, you know if you've read any of his emails, is not a native English speaker; correct?
A. I don't know his -- I don't know. It's hard to tell from quotes.
Q. If you've read four or five of his emails it's pretty easy to tell.
MR. MOSKOW: Object to form.
MR. SCHMIDT: Mr. Moskow would probably stipulate to that.
Q. Do you know what he meant when he said the no monitoring idea/claim?
A. It appears that, you know, the paradigm of which they were following is that

HARVEY

no monitoring is needed. And, you know, this doesn't necessarily fall within that vision.
Q. Okay. Here's I guess what I'm trying to get at, doctor. You could have a marketing claim that there is no monitoring; right?
A. Yes.
Q. But you could also have a scientific idea that monitoring is not appropriate; correct? Or required?
MR. MOSKOW: Objection to form.
A. The second, yeah, you could say that. Yes, yes, you could.
Q. And, in fact, you've seen in the documents and you've seen in the testimony many scientists inside Boehringer and outside Boehringer who have advanced the scientific view that monitoring is not required; correct?
A. Yes.
Q. This email reflects a scientist advancing the view that no monitoring is required; correct?
MR. MOSKOW: Objection to form.
A. I mean, this -- the document states who said what and, you know, the concern is --

HARVEY

well, can you reask the question?
Q. You see that Dr. Clemens is responding to Mr. Kannan; right?
A. Yes.
Q. And his response indicates that it's Mr. Kannan who's asked about a bedside device; correct?
A. Correct.
Q. It's Dr. Clemens who says this would go against our views on monitoring; correct?
A. Yes.
Q. So at least in the context of this email, the person expressing the views that monitoring is not required is the scientist, not marketing; correct?
A. Yes. And that -- how's that important?
Q. He actually expresses that in response to a request from the marketing person about a device; correct?
A. That's what appears at -- to say.
Q. So the marketing concern in this email is, is there a device; correct?
A. Yes.

HARVEY

Q. The scientific response is, that goes against our views on monitoring; correct?
MR. MOSKOW: Objection to form.
A. So the person with the title of marketing has one position; the person with the title of scientist has the other. They both work for the company where the common goal is to advance the company position.
Q. Is one of Boehringer's goals to have safe, scientifically supported medicines?
MR. MOSKOW: Objection to form.
A. One of the goals was to have a product with no monitoring that was determined to be the priority prior to seeing the RE-LY data.
Q. Move to strike as nonresponsive. Was one of the goals of Boehringer to have safe, scientifically founded products --
MR. MOSKOW: Objection to form.
Q. -- as you read the documents?
A. Can you clarify "safe, scientific"?
Q. You don't know what that means?
A. They -- they -- I know that they wanted -- you know, the goal is to have a

HARVEY

product that is based upon the data and where the benefits outweigh the risks.

Q. Okay. I'll take that answer. All I'm asking is in the context of this email, the person asking about the device is a marketing person; right?

A. Yes.

Q. The person saying such a device is contrary to the views of -- that no monitoring is required is a science person; right?

MR. MOSKOW: Objection to form.

Q. Correct?

A. Yes. And they all work for the company.

Q. But this not an instance where the scientist is saying we should have a device and the marketing person is saying that goes against a marketing claim; correct?

A. Yes.

Q. You quote an email from Martin Feuring on page 37.

A. I -- I --

Q. Do you see that?

A. I haven't fully answered the question

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because the -- instead of addressing the scientific issue of the need for a bedside monitoring device, the reply was this goes against our no monitoring claim, not that there would be no utility or no improvement in benefit/risk. So regardless of who said what, the reply to a valid question was the goal of no monitoring.

Q. Move to strike that as nonresponsive.

A. Of course.

Q. Look with me, if you would, at page 37, please.

Do you see that you quote an email from Dr. Feuring on page 37?

A. What line?

Q. 107, the latter part of 107.

A. Yes, I do.

Q. This is him agreeing to the wording that includes the word "over dosage range."

Do you see that?

A. Yes, I do.

Q. Is it important for you when you quote little snippets like this or soundbites like this from company documents that you

HARVEY

understand the full context?

A. I agree that I -- that I do.

Q. Is that important --

MR. MOSKOW: Objection to form.

Q. -- to understand the full context of a discussion like this before quoting those soundbites?

A. Yes, I think it is important to understand the full context.

Q. What was the further discussion about whether that was the appropriate wording?

A. Are you questioning the quote?

Q. I asked you what was the further discussion that day about whether using the phrase "over dosage range" was appropriate.

MR. MOSKOW: Objection to form.

Q. Was there --

A. Would you like to show me that document? Out of 44,000 patients, you're asking me what occurred just before and just after a quote?

Q. Did -- did you look at it?

A. I did look at it.

Q. So what --

HARVEY

A. I read before and after and I chose the part that I felt represented the idea that I wished to represent.

Q. Well, I get that. That's clear. I want to talk about the facts, not the idea you wished to represent.

Factually, did you look at whether there was an alternate email string that had further discussion about whether this was appropriate wording?

MR. MOSKOW: Objection to form.

A. Yes, I looked at many emails.

Q. Okay. And what --

A. And yet that wouldn't change what was said in this email.

Q. Sure. What did the further email say about whether that was the appropriate verbiage, that there was an over dosage range?

A. You would have to show me the email. I can't remember every email that was sent at BI, especially with the ultimate goal of having no monitoring, so --

Q. What did Dr. Feuring testify about whether this was, in fact, his final views on

HARVEY

whether that was appropriate wording?
A. Can you show me a document?
Q. Did you read Dr. Feuring's testimony?
A. I did look at Dr. Feuring's testimony.
Q. What do you remember him saying about whether he ultimately believed that was the correct verbiage, over dosing range -- over dosage range?
A. What I remember reading of his testimony was consistent with this quote.
Q. Did you see his testimony where he said "I'm not a native English speaker"?
A. Yes. I'm not sure how that has a bearing on it.
Q. Did you -- well --
A. Yes.
Q. -- you've probably never written in German; right?
A. No, but -- but when information's provided to FDA in English saying that you're not a native English speaker is never the excuse for having information, you know, given that's not accurate.

HARVEY

Q. I agree.
A. That's not -- that's not -- whether it be Japanese or whether it be any language.
Q. You don't need to list every language in the world.
A. Okay.
Q. Was this information ever provided to the FDA? It was not, was it?
A. What's your question?
Q. Was this verbiage about an over dosage range over provided to the FDA?
A. I don't -- I don't -- no, I don't think it was provided in an sNDA for a labeling supplement.
Q. It wasn't provided in any form, was it?
A. Are you -- are you asking me or telling me?
Q. Both.
MR. MOSKOW: Objection to form.
Q. I'm saying it was not. Do you agree with me that it was not provided to the FDA?
A. I don't know everything that was provided to the FDA because it might have just

HARVEY

been provided in the IND or slipped in somewhere in the annual report.
Q. And, in fact, do you know that it's correct that different language that was agreed to by everyone who was part of this email chain was, in fact, provided to the FDA?
MR. MOSKOW: Objection to form.
Q. That this language was corrected and the correct language was provided to the FDA?
MR. MOSKOW: Objection to form.
Q. Do you know that?
A. Provided to the FDA in what submission?
Q. In any form, doctor. I'm not fussing over the form, I'm just asking you. Do you know that this language that you have cited in your report about an over dosage range was both corrected, agreed to by every participant on the email, and then, once corrected and agreed to by every participant in the email, was provided to the FDA. Do you know that?
MR. MOSKOW: Objection to form.
Q. Just yes or no. Do you know what I said is true?

HARVEY

A. And I know what the label looked like after the process.
Q. This had nothing to do with the label. It had to do with the Hemoclot submission. You know that. Right, doctor?
A. So I -- I -- I do not know what specifically was submitted to FDA as far as a change in wording from what was in this email.
Q. Am I wrong that this wording was corrected?
MR. MOSKOW: Objection to form.
Q. Let me ask it differently. Am I correct that this wording was corrected? Yes or no.
MR. MOSKOW: Objection to form.
Q. Or I don't know.
A. I don't know.
Q. Am I correct that it was agreed to by every participant on the email? Yes or no or you don't know?
MR. MOSKOW: Object to form.
A. I don't know. It was difficult to tell from the email chain whether there was agreement or not or people just stopped

HARVEY

responding.

MR. SCHMIDT: Okay.

THE REPORTER: Let's take a break.

THE VIDEOGRAPHER: Off the record at 6:45.

(Recess taken.)

THE VIDEOGRAPHER: Here begins media number 6 in the video recorded deposition of Dr. Brian Harvey. We're back on the record at 6:52.

(Harvey Exhibit No. 25 was marked for identification.)

BY MR. SCHMIDT:

Q. I've marked as Exhibit 25 that email chain I was alluding to, and I'll direct your attention, if I may, to page 2 of the email where Sandy -- Sandra White from the company that makes Hemoclot or the company that was helping to seek approval of Hemoclot writes to Martin Feuring, Michelle Kliewer, and Andreas Clemens.

Do you see that where she begins "Martin, thank you"? Do you see that?

MR. MOSKOW: Can you orient us to

HARVEY

this? This is a different email than the one that was cited. Is that correct?

MR. ANDERSON: Yes, it is.

MR. SCHMIDT: It's a different chain with common parts to the chain.

A. "Martin, thank you."

Q. Yes.

A. That would be correct to say.

Q. And so here at the bottom we see the November 22, 2010 email from Sandra White working to secure approval of Hemoclot to Martin Feuring and others, and you quote language from that email in paragraph 26 -- I'm sorry, on page 26 of your report where she asks "Would it be correct to say," and she references an over dosage range; correct?

This is that same email, at least Dr. White's portion of it.

A. Yes.

Q. And then, as sometimes happens when you have an email, Dr. Feuring sent one response back. And what we see here is a different response from Dr. Clemens. Do you

HARVEY

see that right above the response, the -- the email from Dr. --

MR. MOSKOW: May I help the witness?

MR. SCHMIDT: Sure.

THE WITNESS: I don't have any --

Q. Do you see above?

A. It's above?

Q. Yes. Do you see above, Dr. Clemens separately responds to Ms. White in addition to the email from Dr. Feuring that you cited?

A. So where he says "I have wording like in the label of Canada"?

Q. Uh-huh. Do you see where he separately responds to her --

A. Yes.

Q. -- copying Dr. Feuring, copying Michelle Kliewer, copying Ms. White?

A. Yes.

Q. And he says: "I would like to have a wording like in the label of Canada," and then he quotes it.

Do you see?

A. Yes.

HARVEY

Q. "Patients are at a higher risk of bleeding and not overdosing."

Do you see that?

A. Yes.

Q. So he doesn't want to use "overdosing." He wants to use "patients are at a higher risk of bleeding"; correct?

A. Yes.

Q. She says above that: "Dr. Clemens, thank you. I agree."

Do you see that?

A. Yes, I do.

Q. And do you know that Dr. Feuring testified that he also agreed with that language --

MR. MOSKOW: Objection to form.

Q. -- once he saw Dr. Clemens' email after his?

A. Yes.

Q. You did know that?

A. Yeah. And this is from November 2010?

Q. Yes.

A. And when was the 510(k) cleared?

HARVEY

Q. My question --

A. Doesn't, I -- I -- I'm not -- you're not going to talk about that? Okay.

Q. In fact, I'll move to strike "and this is from November 2010" because that really took us off on a tangent.

So does this show to you that Dr. White's or Ms. White's language was corrected by Dr. Clemens and she agreed to the correction and Dr. Feuring agreed to the correction?

MR. MOSKOW: Objection to form.

A. In which email are you referring to?

Q. Exhibit 25 where Dr. Clemens corrects it and she agrees to the correction, and then he agreed in his deposition to the correction.

MR. MOSKOW: Objection to form.

A. And -- and are we on 26 now or 37 of my report?

Q. We are on Exhibit 25.

A. Right, but you're comparing back to my report and you're asking me to look at a different chain of emails regarding -- you know, then what I quoted.

HARVEY

Q. Yes, and that's my point. Did you -- had you seen Exhibit 25 before I showed it to you just now?

A. The November 22, 2010 email?

Q. Uh-huh. Other than her original email had you seen Dr. Clemens' response to her email and her response back saying she agrees with Dr. Clemens?

A. I remember reading about the -- the reluctance to use the word "overdosing."

Q. Did you see this email, sir?

A. Yes, I believe I -- that was one of the ones I saw because I was looking for it at the 510(k) preIDE review.

Q. And so my question is the language you quote in your document in your report on page 27 where she talks about an over dosage range and Dr. Feuring agrees to her wording, do you see that?

A. Yes.

Q. Do you agree with me that Dr. Clemens subsequently corrected her wording to say patients are at a higher risk of bleeding and she agreed to it?

HARVEY

MR. MOSKOW: Objection to form, asked and answered.

A. And I think the focus of my quote was not the word "overdose," it was the range. And so he didn't negate talking about the range, he just objected to the word "overdose" and wanted to substitute "higher risk of bleeding."

Q. Let me try again. Move to strike as nonresponsive. Do you agree with me that Dr. Clemens corrected her overdosing wording and she agreed to the correction?

MR. MOSKOW: Objection. I don't want to coach the witness but you're using a word in that question that I think is -- is improper for purposes of this line.

Q. Sir?

MR. SCHMIDT: For the record, the witness isn't even looking at the document I'm asking him about.

A. No, I -- I'm waiting for you to ask a -- the question again.

Q. I asked the question again. I'll ask it one more time.

HARVEY

A. Okay.

Q. Do you see in Exhibit 26 that when Ms. White proposed language that referred to an over dosage range, Dr. Clemens corrected it by saying it should be "patients are at a higher risk of bleeding," and she agreed to the correction?

MR. MOSKOW: Objection to form, asked and answered.

A. And what he objected to was not the range but the word "overdosing," and he replaced that with "higher risk of bleeding."

Q. Right. So let me ask my question again because I think you're saying what I'm saying but just not answering me.

Do you see where she proposes language that references an over dosage range, he corrects it to say instead "patients are at a higher risk of bleeding," and she agrees to his correction?

MR. MOSKOW: I'm going to object to the question. The form is wrong. It uses the word "corrected." The witness has answered it three times, and I'm

HARVEY

going to instruct him not to answer it. You want to go to the judge on this one, go to the judge. He's not going to answer that again.

MR. SCHMIDT: Move to --

MR. MOSKOW: It's --

MR. SCHMIDT: -- strike all of --

MR. MOSKOW: It's -- it's --

MR. SCHMIDT: -- his opinions on this email.

MR. MOSKOW: It's almost 7 o'clock. We have agreed to extra time, but for you to keep asking a question with the word "corrected" as opposed to "changed" or "it's different" is a qualitative question. The witness has answered to the best of his ability that the word was changed.

MR. SCHMIDT: He's agreed with me about something else. He's referred to his report, and -- but I'll move on. You've given your instruction.

BY MR. SCHMIDT:

Q. Are you going to follow that

HARVEY

instruction, doctor, knowing that we will move to strike any testimony based on this document?

Are you going to follow that instruction, doctor?

A. I'm going to follow the instruction.

Q. Okay. You've seen reference in documents where marketing people at Boehringer thought there might actually be a competitive advantage to monitoring and to doing dose titration; correct?

A. I saw some emails that -- that by enhancing the benefit ratio there actually could be a market advantage.

Q. Okay. Did you ever see anywhere in documents where the scientists said we think monitoring makes sense, and marketing said we don't want to do that from a marketing perspective?

A. I saw emails where the issue of testing was raised and the response was it's not in keeping with our no monitoring policy.

Q. Right. And I know what you're talking about when you say that. The examples I've seen the people saying that are the

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scientists. And so come back to my question, which is very precise.

Have you seen instances where the scientists said we think monitoring is appropriate, and the marketing folks said no, we can't do that because of our marketing goals?

A. I can't answer that because I disagree with the premise. When -- when I was in industry, just because someone had a certain title didn't necessarily mean they'd have a certain point of view. And there was -- always can be group think within an organization. And regardless of your role, you can -- you can unite behind a common goal.

So which role the person had and what they said, the thing is if they work for the company and that was a belief, and every attempt for testing then didn't come to fruition, that to me is what said something.

Q. I didn't ask any of that so let me ask my question.

Did you see an instance where scientists at BI said we want to do monitoring,

HARVEY

we will recommend some form of monitoring or testing, and the marketing people said no, we won't do that because that's inconsistent with our marketing goals? Did you see such an instance?

MR. MOSKOW: Objection to form.

A. So when I read the emails, I didn't note whether someone was, quote, a scientist or, quote, a marketing person but I did read emails where the response was this is not consistent with no monitoring.

Q. Did you see an instance where anyone expressed the view that monitoring should -- you saw instances -- strike that.

You saw instances, and we've looked at some of them, where people said their scientific view was that monitoring didn't make sense; right?

A. There were differences of opinion, that's correct.

Q. You saw instances where people said as a scientific matter they didn't think monitoring made sense; correct?

A. Yes, correct.

HARVEY

Q. And there's no one you can point me to who their ultimate opinion was we should be doing monitoring, correct, at BI?

A. At the time of submission of the NDA?

Q. Ever. Is there any --

A. Isn't Paul Reilly a member of -- in -- in some of the consensus work?

Q. Is it your understanding from Dr. Reilly's testimony that his current view is that there should be monitoring?

A. Oh, I was -- I was basing it based upon the publications.

Q. And the publications don't say there should be monitoring. They talk about whether there's a hypothetical sweet spot; correct?

A. Correct.

Q. Okay. So is there any BI employee you've seen who their ultimate opinion after analyzing the data was monitoring was appropriate?

A. No.

Q. Is there any time you saw a marketing person specifically say we can't talk about monitoring because it goes against a no

HARVEY

monitoring marketing claim?

A. I didn't see that in an email.

Q. You talk about a prescriber guide and a patient alert card in Europe on page 104 of your report.

So before you get there, turn with me to page 73.

A. To?

Q. 73, please. And specifically, footnote 56. In footnote 56 on page 73 you make reference to a jokey email chain between Allison Blouse at the FDA and Michelle Kliewer at BI.

Do you see that?

A. Yes, I do.

Q. I think you've interacted with Ms. Blouse; is that correct?

A. Some interactions over the years, likely when I was at Sanofi or Pfizer.

Q. Both within and without -- both inside and outside of the FDA, or just outside the FDA?

A. I -- I don't remember any direct interactions at FDA.

HARVEY

Q. Did you always find her to be professional and appropriate in your interactions with her?

A. I never had any instance to question that.

Q. You cite some regulations and a conflict of interest statement in this footnote?

A. Yes.

Q. Are you offering any opinion that either Ms. Kliewer in this email chain or otherwise or Ms. Blouse did anything inappropriate?

A. No, I'm just providing the references.

Q. You're not suggesting that there's an improper solicitation of employment or anything like that, are you?

A. I think I just wanted to put the email in context.

Q. In fact, I think you say this appears to be innocuous banter; right?

A. Yes.

Q. And you stand by that statement;

HARVEY

right?

A. I -- I stand by my report, that's correct.

Q. Page 96 -- I'm sorry, page 97, you cite a quote from Dr. Valentine.

Do you see that?

A. Which paragraph?

Q. First one, 263.

A. Okay.

Q. Do you see where you quote an email from him in the block quote?

A. There might be.

Q. Yes.

A. Okay.

Q. And you attribute to him the view that there was a need to identify, monitor, and titrate certain patients falling outside the 10th to 90th percentiles.

Do you see that?

A. Yes.

Q. Do you know that Dr. Valentine actually did not endorse the 10th to 90th percentile?

MR. MOSKOW: Objection to form.

HARVEY

A. Endorse in what forum and at what time?

Q. Ever. Did he ever endorse the 10th to 90th percentile in your -- in your -- to your knowledge?

A. I -- I'm quoting what I read.

Q. And there's nothing in that quote about the 10th to 90th percentile; right?

A. Yes. And so what's the question?

Q. Have you seen him ever endorse the 10th to 90th percentile, as your text suggests?

MR. MOSKOW: Objection to form.

A. In the quote, he's talking about, you know, thrombin time in high-risk patients.

Q. Do you know if he ever endorsed the 10th to 90th percentile being the appropriate range? Yes or no.

A. So your -- the question is not whether or not he felt that there needed to be some sort of testing, it's whether he endorsed the specific recommendation of 10th to 90th?

Q. Correct.

A. Okay.

Q. Do you --

HARVEY

A. There -- there's --

Q. -- know if he did?

A. There's no way to tell from that information on the page.

Q. And do you know what Dr. Valentine's ultimate informed view was on whether there was a optimal range?

A. And you mean by -- to clarify, ultimate meaning is -- his affidavit, his -- his testimony?

Q. Uh-huh, or his publications or any other source. Do you know what his ultimate view after he -- I think if we look at the quote you have on page 97, this sounds like that kind of speculation. "There might even be a reason to tailor the dose based on measurements." Right?

A. So it -- my --

Q. Do you --

A. My --

Q. -- know --

A. -- thought --

Q. -- what his --

A. -- was -- was that he -- he believed

HARVEY

that there was some testing that -- some high-risk patients that would benefit from testing.

Q. My question is, do you know if that was his opinion after he had finished considering all the data in reaching his most informed view?

MR. MOSKOW: Objection to form.

A. Yeah, I know that --

Q. Do you know? Yes or no.

A. No, I don't.

Q. Look with me, if you would, at page 104. You reference something called -- in paragraph 286 something in Europe called the prescriber guide and the patient alert card.

Do you see those?

A. Yes.

Q. Can you point me to any specific information that either the prescriber guide or the patient alert card contains that is not reflected in the Pradaxa U.S. label or the Pradaxa U.S. medication guide?

A. Yeah, I would want to look at the card, but from memory, they talk about the 110

HARVEY

dose and then how to go from -- you know, go from the 150 to 110. And, of course, there is no 110 dose in the U.S. That's a glaring example of a difference.

Q. Fair enough. It would be illegal for the -- for Boehringer to talk about the 110 dose, at least in stroke prevention patients in the U.S.; correct?

A. Not without submitting the data that FDA outlined back in 2011, that's correct.

Q. Right. And so other than information they're legally barred from talking about, is there any information in the prescriber guide in Europe or the patient alert card in Europe that is not in the medication guide or the label in the U.S.?

A. There were some details on that card that I remember being informative that I do not remember from the U.S. label. I would have to look at the actual guide. It was a very well thought out presentation and I think would have provided value to the physicians there, and it's unfortunate that our physicians don't have that same -- same benefit.

HARVEY

Q. Have you compared the U.S. label and the U.S. medication guide to European warning materials to identify information that's in the U.S. materials but not in the European materials?

A. No, that's not been part of my evaluation.

Q. Okay.

MR. MOSKOW: Just about done?

MR. SCHMIDT: Yeah.

Q. On page 98 of your report you cite a letter that the FDA sent to Boehringer in May of 2013.

Do you see that?

A. Yes.

MR. SCHMIDT: And why don't we go ahead and mark that. You understand that that's something called a change of opinion letter; right?

MR. MOSKOW: Objection to form.

THE WITNESS: I know it was a advertising and promotion letter.

(Harvey Exhibit No. 26 was marked for identification.)

HARVEY

BY MR. SCHMIDT:

Q. Did you know it was a change of opinion letter?

MR. MOSKOW: Objection to form. It's a "yes," "no," or "I don't know".

A. I would need to see the letter.

Q. I've marked as Exhibit 26 a copy of the letter. Is this, in fact, the letter you cite and quote on page 98 of your report?

A. I mean, it's from the division of advertising and promotion. Now, the -- their intent is to change their opinion.

Q. Sir, my question was just is this the letter you cite at page 98 of your report?

A. Yes, I -- yes, it is.

Q. Is this a change of opinion letter?

A. Well --

MR. MOSKOW: Objection to form.

A. -- so when -- when I look at letters, they usually say Warning Letter or Untitled Letter, Notice of Violation. This doesn't say Change of Opinion Letter. It says it in the body of the letter.

Q. It doesn't say Warning Letter; right?

HARVEY

A. It does not say Warning Letter.

Q. It's not a warning letter; right?

A. It's not a warning letter.

Q. It's not an untitled letter; right?

A. It doesn't say Untitled Letter.

Q. It's a letter telling Boehringer that we have thought about a view we previously endorsed and we have changed our mind and we want you to change your materials accordingly; correct?

MR. MOSKOW: Objection to form.

A. That is correct, and that's how I represented it in my report.

Q. It would be false, though, to call this a warning letter; correct?

MR. MOSKOW: Objection to form.

A. Yes.

Q. The FDA issues warning letters up to dozens a year; right?

Do you know how many warning letters the FDA issues to companies every year, ballpark?

A. The number has gone down but it still is certainly over a dozen in advertising and

HARVEY

promotion.

Q. Did you receive warning letters when you were at companies?

A. Yes, I did.

Q. Can you quantify how many you received?

A. I received -- so two when I was VP at Pfizer based upon actions that took place before I took over the duties. But there were two during my three and a half years and nothing during my time --

Q. At Sanofi?

A. -- at Pfizer. And I wasn't directly involved with advertising and promotion at Sanofi because that was the U.S. affiliate and I was part of global.

Q. Okay. Do you take a warning letter from the Food and Drug Administration seriously?

A. Oh, very much so.

Q. Did you see any warning letters that BI received for Pradaxa?

A. No, I did not review any specific warning letters.

HARVEY

Q. They didn't receive any, did they?
MR. MOSKOW: Objection to form.
A. No, I -- I didn't see them in my -- my review.
Q. They also didn't receive any untitled letters, did they?
MR. MOSKOW: Objection to form.
A. No.
Q. And so the jury understands, an untitled letter is a way of pointing out a concern that the agency has, often about promotional materials; correct?
A. That's correct.
Q. And a warning letter is an even more serious way of pointing out that concern.
A. That's correct.
Q. And as best you know, Boehringer never received an untitled letter for its promotion of Pradaxa or a warning letter for its promotion of Pradaxa; correct?
A. That's correct.
Q. This is something different. This is saying we previously approved this messaging, now we'd like you to change it, having thought

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further about it. You can continue giving the same numbers you were giving, but we want you to GI more context; correct?
A. That's correct, with the -- with the goal of having BI change its advertising and promotion material.
Q. And BI did that immediately, didn't it?
MR. MOSKOW: Objection to form.
Q. If they didn't, we'd be looking at the warning letter they received for not doing so; correct?
MR. MOSKOW: Objection to form.
A. That would be correct.
Q. And they didn't -- they changed it immediately as best you know; right?
A. I have no information to say otherwise.
Q. Okay.
A. And -- and I characterized this as such in my report as a -- FDA-issued a letter.
Q. Last line of questions I'm going to ask you about, page 70 -- 79, you talk about the Hemoclot assay. And it goes back to some

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of those emails with Ms. White.
You understand that Ms. White was not a BI employee; right?
A. I understand that she worked for the company that was developing the assay.
Q. Hemoclot is not a BI product, is it?
A. That's my understanding.
Q. You say on page 79, the last carryover paragraph: "In my opinion, BI did not adequately support the FDA review process of the Hemoclot assay in the U.S."
Do you see that?
A. Yes.
Q. Hemoclot was produced by an entirely independent company; right?
A. It was an -- a separate company, that's correct.
Q. No ownership interest by BI in either Hemoclot or the company?
A. I -- I don't know its -- its lineage of -- as a company, but I take that at face value.
Q. You know Hemoclot is approved in many other countries in the world, including in

HARVEY

Europe?
A. Yes, that's -- I've read that.
Q. Is there any support that BI provided to get Hemoclot registered in any country outside the U.S. that it failed to provide in the United States?
MR. MOSKOW: Objection to form.
A. Can you rephrase the question? Because --
Q. Sure.
A. -- it's my understanding that it's still not FDA cleared in the U.S., Hemoclot.
Q. Is there any support that BI provided to the company making Hemoclot to help it get approved in other countries that it failed to provide in the United States?
A. I don't know.
Q. Okay. So when you talk about not adequately supporting the FDA review process, you can't point me to anything BI was willing to do in other countries and not willing to do in the U.S.; correct?
MR. MOSKOW: Objection to form.
A. The medical device approval process

HARVEY

and clearance process is different in the U.S. than in --

Q. Sure.

A. -- the rest of the world. The 510(k) is submitted on a 90-day clock so you -- normally doesn't take that long to get a 510(k).

Q. My question is simply when you fault BI for not doing enough to help Hemoclot in the U.S., you can't point to anything it did elsewhere that it didn't do in the U.S.; right?

MR. MOSKOW: Objection to form.

A. That is correct. I just know what didn't get accomplished in the U.S.

Q. Right. And do you -- do you take issue with just the FDA didn't see the value of Hemoclot in the way that other regulatory agencies did?

MR. MOSKOW: Objection to form.

A. FDA standard, they need to have data to support cutoffs, and it's my understanding that that data was never generated and supplied.

Q. Do you know if any data on plasma

HARVEY

concentration levels was given by the Hemoclot manufacturer to the FDA?

A. I don't know, because that wouldn't directly impact -- you know, they would be looking for data generated by the machine. If they're looking to clear the machine, they need data from the machine.

Now, correlating that with drug levels would be helpful, but that's only part of the -- part of the process.

Q. Boehringer doesn't control that data you just talked about; right?

A. The machine can be used by -- if -- if it's approved outside the U.S., then any site where it's a valid machine can be -- you can use it to test patients who are on Pradaxa. I mean, there's a way to generate --

Q. Let me ask --

A. -- the data even if you don't own the machine.

Q. Let me ask you this question. Is there data BI should have provided to the FDA regarding Hemoclot that it did not that you can point me to?

HARVEY

A. The data that FDA felt it needed to clear the device didn't get supplied to FDA --

Q. We know --

A. -- to result in a clearance.

Q. We know that. That's a fact.

A. Right.

Q. My question is, can you point me to any data that BI had that would have helped secure approval that BI did not provide to the FDA or to Aniara, the Hemoclot manufacturer?

A. I don't know of data that they had but didn't supply, it was that they didn't generate the data.

Q. Okay. On page --

MR. MOSKOW: I'm going to --

Q. The data was good enough in other countries; right?

A. Okay, it -- there's a different system for device evaluation --

Q. Sure.

A. -- in other countries.

Q. So it was --

A. You can't compare a CE mark and a 510(k) clearance. They're apples and oranges.

HARVEY

Q. Last question on this. You -- on page 77 of your report, you recount some of the back-and-forth between Aniara and the Hemoclot company and the FDA, and you cite at the bottom of the page a May 6, 2011 response from the FDA.

Do you see that?

A. Yes, I do.

Q. And the FDA response is: "Be advised a common drawback in any direct thrombin inhibitor testing method is the lack of a well-defined therapeutic concentration ranges."

Do you see that?

A. Yes, I do.

Q. Is that a true statement or a false statement, in your view?

MR. MOSKOW: Objection to form.

A. That's a true statement.

MR. SCHMIDT: Thank you. That's all I have.

MR. MOSKOW: Why don't we stay where we are? I have only a very few questions and then we can finish up.

HARVEY
EXAMINATION
BY MR. MOSKOW:
Q. Doctor, if you would continue to look into the camera and talk to the jury even though I'm right beside you, doctor, earlier today you had a discussion concerning an email chain between Drs. Connolly and Reilly.
Do you recall that?
A. Yes, I do.
Q. And you used the word "speculation."
A. Yes.
Q. What did you mean by the use of the word "speculation" in that context?
A. I used the word "speculation" in -- in sort of a vernacular sense, in sort of a common everyday sense where the back-and-forth between individuals. And, you know, now as I think about the exact meaning of speculation, to be more precise, you know, it really wasn't speculation because if it's a conversation based upon data, then it really is a debate over the interpretation of that data. And by calling it speculation, that would be -- you know, it's not a fair representation of what

HARVEY
they were doing. There was a -- a debate over the data in a preliminary setting in order to come to a consensus for a final conclusion.
Q. And have you seen data in the peer-reviewed medical literature that supports the email communication between Dr. Connelly and Dr. Reilly that we were just talking about?
A. Yes, yes, I have.
Q. And give me an example of somewhere in the peer-reviewed medical literature where you've seen that.
A. Well, in -- in some of the recent publications there's been a supporting evidence. And I can go through those, but it's a -- it's --
Q. Let me ask the question differently.
A. Sure.
Q. Are you aware of a paper published in July of 2016 by Reiffel, Reilly, and others which reflected a consensus opinion of the Cardiac Safety Research Consortium?
A. Yes, I do.
Q. Is that a paper that plays a role in the formation of your opinions?

HARVEY
A. Yes, it does.
Q. Why is that?
A. Well, because it's -- it's the best thinking at the time of the experts based upon their data available. And there's some discussion about the utility of drug levels, but part of that is just based upon at that time being able to obtain Pradaxa drug levels wasn't widely available.
Q. Okay. And does the Reiffel paper indicate a therapeutic range for dabigatran concentration?
A. Well, there is that discussion.
Q. And what do you recall that range being?
A. I would have to refer to the paper, but it's certainly consistent to the 50 to 150.
Q. And -- and if I represented to you that on page 76 of the Reiffel paper specifically identifies a sweet spot between 50 and 150, is that consistent or inconsistent with your recollection?
A. That is --
MR. SCHMIDT: I object --

HARVEY
A. -- consistent.
MR. SCHMIDT: -- to the --
Q. And is the?
MR. SCHMIDT: -- characterization.
THE REPORTER: I'm sorry, who's speaking?
MR. SCHMIDT: I objected to the characterization.
THE REPORTER: And now your answer, sir?
THE WITNESS: My recollection of the paper was that they mentioned a sweet spot of 50 to 150.
BY MR. MOSKOW:
Q. And finally, doctor, you've been asked over eight hours of questions by opposing counsel today. There's been some back-and-forth. You've reviewed 26 exhibits. You've been asked about other items that weren't presented to you. Is there anything about the proceedings today that impacts the opinions that you've expressed in your report that was identified as Exhibit 1 to this proceeding?

HARVEY

A. Well, I -- I wrote my report to the best of my ability and the understanding that I had of the various documents. I reviewed the report in preparation for today's deposition and was in agreement with what I was reading. And now after the -- the questioning by opposing counsel, you know, I stand by the body of my report and fully support the conclusions I came to.

Q. And, doctor, in that regard you said you -- you reviewed documents. This is a 120-page report. True?

A. Correct. True.

Q. In the schedules that were attached you identify hundreds and hundreds of documents. Is that fair?

A. Yes.

Q. Are you able to estimate the number of pages that you reviewed both in preparing and drafting your report and in preparing for your deposition today?

A. It -- it would just -- you know, there -- there were so many pages and so much information, and you're -- it -- it's not

HARVEY

unexpected that it took 200 hours to review materials and to write the report.

Q. And I appreciate that answer. It wasn't the specific answer to my question.

A. Oh.

Q. I have some sympathy for some of Mr. Schmidt's points earlier today. My question was more basic.

Are you able to estimate the total number of pages that you reviewed of company documents, medical literature, deposition transcripts?

A. As far as what? Thousands or --

Q. Yeah, thousands.

A. -- tens of thousands? It's well into the thousands.

Q. Okay. My very last question. You referred to the CCDS, or company core data sheet, a number of times during the course of today's proceeding. Is that fair?

A. Yes.

Q. Why do you keep bringing up the company core data sheet?

A. Well, I had a lot of experience at

HARVEY

Pfizer with their company core data sheet and a lot of thought went into Pfizer's core data sheets and the -- all of the information, all the data that supported that position. And when there was a position in the company core data sheet, you know, they fought pretty hard to make sure that the labels around the world were consistent.

Q. Did you identify during the course of your preparation of your report and for your testimony how people at Boehringer Ingelheim viewed the company core data sheet?

MR. SCHMIDT: Objection, foundation from this witness, speculation.

Q. For example, did you -- let me rephrase the question.

Sir, in preparing your report and in preparing to testify today did you review deposition testimony of Drs. Kreutzer, Drs. Epperla and Dr. Barner (phonetic) as to their views regarding the value of the company core data sheet?

A. Yes.

Q. And how, if at all, did the review of

HARVEY

that testimony inform your belief as to the importance of the core company data sheet and the information that should be conveyed to clinicians in the United States?

A. Well, I think it's clear that there's a belief that the core company data sheet is an important document.

I guess what I have trouble reconciling is that FDA gave a path forward back in 2011 on how, you know, the 110-milligram dose could get approved, and that would be a way to improve the harmony of -- of the core data sheet in the U.S. label, and that avenue wasn't actively pursued.

So although there's a -- a -- a verbal belief that it's important, some of their actions in trying to generate the data needed for changes to the U.S. label and that were, you know, then, you know, done in -- in Europe, you know, that hasn't yet happened as of to this day.

MR. MOSKOW: No further questions.

HARVEY
EXAMINATION
BY MR. SCHMIDT:
Q. Just a few follow-ups, doctor. Did you change any of your testimony from your questions and answers with me based on what Mr. Moskow just asked you?
A. I don't think I did. I think I -- I believe in my report and stand by my conclusions.
Q. And you're not changing any of the testimony you gave with me?
A. I don't think anything I just said did that.
Q. Including what you said about speculation?
A. I don't think I was speculating when I said -- you know, there are some people at BI who believed that the core data sheet's important.
Q. And do you --
A. I don't think that's -- that's -- and -- and so I -- I stand by that -- that there are folks at BI who believe that the -- that's an important document.

HARVEY
Q. Do you stand by your testimony when you and I were talking about speculation? Yes or no.
MR. MOSKOW: Objection to form.
A. Which -- what's -- I -- I think I've said that speculation is not speculation when it's based on data and that that was a misrepresentation. It wasn't -- the word, that wasn't from my report. I had used that in the characterization of an email. It probably was not an accurate reflection, given the fact that they were debating data in having a scientific exchange, which is not speculation.
Q. Okay. So you're changing your testimony on that point in response to Mr. Moskow's questions?
A. Yes.
MR. MOSKOW: Objection to form.
A. So in --
Q. Yes or no?
A. Yes.
MR. SCHMIDT: Okay. The Reiffel paper, let's mark it so we have it in the record.

HARVEY
(Harvey Exhibit No. 27 was marked for identification.)
BY MR. SCHMIDT:
Q. We have marked as Exhibit 27 the Reiffel paper you were just asked about. Do you recall being asked questions about this?
A. Yes.
Q. Did this paper recommend testing blood levels? Turn to page 82, please.
A. That's the one I'm on.
Q. In the left column right before the paragraph at the bottom that begins "second," it says: "Monitoring NOACs is a way to assess drug levels, actions, or to maximize dose flexibility or ultimately to benefit patient care remains unproven."
Did I read that correctly?
A. Yes, you did.
Q. That's the conclusion of the article; correct?
A. That's in the conclusion section, yes.
Q. And nowhere in this article do they recommend testing blood levels; correct?

HARVEY
MR. MOSKOW: Objection to form.
A. No, they -- they -- they don't give a recommendation. They discuss it.
Q. No, they discuss a concentration and a sweet spot; correct?
A. Yes.
Q. And one -- you understand that there's a relationship between plasma concentration and patient characteristics; right?
A. Yes, I do.
Q. And the closest relationship is between plasma concentration and the patient characteristic of renal function; correct?
A. Can you repeat that?
Q. There's a close relationship between renal function and plasma concentration; correct?
A. There is a relationship, yes.
Q. It's a close relationship, isn't it?
A. I would have to have a definition of close, but yes, there is a relationship.
Q. You know that the Pradaxa label recommends monitoring renal function; right?

HARVEY

A. Yes, that's correct.
Q. And adjusting dose based on renal function?
A. I agree --
Q. Do you agree with --
MR. MOSKOW: Objection, form.
A. -- with that, yes.
Q. Do you have data that tells you -- let's assume this sweet spot discussed in this article of 50 to 150 is correct. Do you have data telling you how many patients with renal function monitoring and dose adjustment nevertheless fall outside that sweet spot, if any?
A. Are you saying from this article, from this article or the --
Q. I'm saying from anywhere in the world.
A. So are you -- are you -- you questioning the paper by the consensus group here?
Q. No.
A. I mean, I don't have any data. The only data I have is what I've been reading.

HARVEY

Q. Let me ask you this. Do you know that if you monitor renal function as recommended in the label and adjust dose as recommended in the label that you end up with any patients who fall outside of a range of 50 to 150 nanograms per milliliter on a consistent basis?
A. That makes sense.
Q. Do you know if that happens at all in the real world, if you monitor renal function and adjust dose that you end up with any patients outside of -- outside of this range of 50 to 150?
MR. MOSKOW: Objection, form.
A. Is the Temple slides and the real-world data publications, is this a -- are you quizzing me from what I remember from those now?
Q. No. Dr. Temple himself -- and let's look at his slides since you mention them. I'll show you as Exhibit 28 the ones that were given in 2015.
Do you see these slides?
A. Yes, I do.

HARVEY

Q. And in these slides he talks about plasma concentrations; correct?
A. Correct.
Q. And on slide 14, the very -- the ultimate slide in his deck, he says maybe no blood level.
Do you see that?
A. "Maybe no blood level."
Q. And he says it may be possible to adjust dose in accordance with the factor that is most critical to the blood level attained renal function.
Did I read that correctly?
A. Yes.
Q. Is Dr. Temple correct when he says that the factor that is most critical to the blood level attained is renal function?
A. Well, that's what he's focusing on. Age is another critical factor. And then he said if that can be done it would be very hard to see why one would be not do it.
Q. Is renal function the most critical factor to blood level, as Dr. Temple says here?
MR. MOSKOW: Objection to form.

HARVEY

Q. Is that a true statement, a false statement, or you don't know?
A. It's not a false statement, but most, most is -- I would have to see how the comparison was done because we all know advancing age is important and we know renal function is important, and they're both independent so it's very hard to say what is most.
Q. So when he says the factor that's most critical to the blood level attained is renal function, do you agree, disagree, or not have a view?
MR. MOSKOW: Objection to form.
A. I agree that renal function's important, as is age.
Q. Do you agree that it's the most critical?
A. I would have to see how he decided to -- to use that, that imprecise regulatory word of "most."
Q. Do you know -- that -- let me go back to my question then. If you adjust dose based on the most -- this critical factor to blood

HARVEY

level, renal function, if you adjust dose based on renal function do you know that you end up with any patients who are outside of a specific target range?

MR. MOSKOW: Objection to form.

A. That would be the study that BI would need to do because if age is an independent risk factor, that even if you adjust for renal function, you still might have patients with advancing age that are increased risk.

Q. And so that's my question. Do you know if that exists? Have you seen any data that tells you if you dose --

A. I haven't --

Q. Let -- let me finish. Have you seen any data that tells you if you adjust based on renal function that there are patients who remain out of the range you think they should be in?

A. I haven't seen adequate data, and -- and BI should test that.

Q. And so one more question on this issue. What's that?

A. And then -- and then of course, the

HARVEY

last quote --

Q. There's --

A. -- this can be --

Q. -- no --

A. It's hard to --

Q. -- question --

A. -- see why --

Q. -- pending, doctor.

A. -- it would not be done. That got left out.

Q. I don't think it got left out. It got put in the label in 2012.

MR. MOSKOW: Objection to form.

MR. SCHMIDT: But -- but that is objectionable because now we're just arguing so let's strike both of what we said.

BY MR. SCHMIDT:

Q. Doctor, even if you could identify a sweet spot, let's say it's 50 to 150, it still might not be a good idea to try to dose adjust to get to that sweet spot if in the real world just because of interpatient variability and challenges of testing even with the best test

HARVEY

in the real world you couldn't reliably measure levels; correct?

MR. MOSKOW: Objection to form.

A. I think that's a valid concern that needs to be tested with further clinical trials.

Q. You made reference in one of your answers to your work at Pfizer. I think you were talking about the company core data sheet. Do you remember that?

A. Yes, I do.

Q. Have you told either the people you work with at Pfizer now or your former colleagues at Pfizer that you're doing this paid expert work for plaintiff's lawyers in this case?

A. No.

Q. Do you have any objection to us reaching out to them about it?

A. No.

MR. MOSKOW: Objection to form.

A. I looked over my severance agreement. There's nothing preventing me from doing this work on Pradaxa.

HARVEY

Q. You specifically consulted your severance agreement on that point?

A. Well, I -- I have it right there on my desk and I looked at it to make sure.

Q. Why?

A. What?

Q. Why?

A. Why do I have it on my desk?

Q. No, no, no. Why did you look at it in connection with your work here?

MR. MOSKOW: Objection, form.

A. Because I -- I just want to make sure that nothing I do conflicts with anything else I'm doing. I mean, I looked at everything else I'm doing just to make sure that it's not a conflict.

Q. Were -- did you think there was a possibility of a conflict?

MR. MOSKOW: Objection to form.

A. No.

Q. Okay. But you nevertheless consulted the agreement?

A. As -- as part of my routine work as Brian E. Harvey LLC I consult all the various

agreements when I start a new project.
Q. What is Brian E. Harvey LLC?
A. That's my individual consulting group.
MR. MOSKOW: Brian.
THE WITNESS: Brian E. Harvey.
Q. You mentioned reviewing thousands of pages of documents.
A. Yes.
Q. Did you select those from a larger set of documents?
A. I had access to all of the documents.
Q. And so how did you pick out those thousands of pages?
A. I went through the Dropbox and opened and looked and read and, you know, developed my report and looked at other documents and -- and tried to work my way through.
Q. And did you -- do you know what the largest set of documents to which you had access to was, like the volume?
A. Was that the 44 -- I mean, there -- there were many, many documents. I mean, everything's listed.

Q. I'll -- I guess that's what I'm wondering. Did you only have access to the documents listed in your reliance lists, in your supplemental list in your materials reviewed?
A. Only? That was a lot of documents.
Q. It's a subset of the total production we have been --
A. Okay.
Q. -- asked to make at plaintiff's lawyer's requests. Did you have access to the full 50 million pages of documents?
A. I know that I would -- had access to the documents that were in the Dropbox. I don't know what subset that is.
Q. We can agree --
A. -- picture.
Q. That's what you identified on your -- I think there were two lists plus a supplemental list.
MR. MOSKOW: Correct. You should ask him whatever your questions are and then I'll -- I can tell you.
MR. SCHMIDT: Why don't we just

mark those two exhibits then.
THE REPORTER: Let's go off the record so I can stand up. Let's go off, Kim.
THE VIDEOGRAPHER: Off the record at 7:44.
(Recess taken.)
(Harvey Exhibit No. 29 was marked for identification.)
(Harvey Exhibit No. 30 was marked for identification.)
THE VIDEOGRAPHER: Back on the record at 7:44.
BY MR. SCHMIDT:
Q. Could you identify for me the exhibit numbers on these two documents I just passed you?
A. Exhibit 29 and 30, and I think one of these was already --
Q. I thought that was the third supplemental list.
A. That may be, that may be.
Q. So are Exhibits 29 and 30 plus the list we were given dated November 29, which I

marked as Exhibit 16, are those the universe of documents you had access to?
A. That's -- I believe so.
Q. Did the lawyers point you to any specific documents or specific parts of testimony?
A. No.
Q. And last question. You talked about the 110-milligram dose.
Do you remember that?
A. Yes, I do.
Q. Is it your understanding that the 110-milligram dose prevents significantly less strokes than the 150-milligram dose?
MR. MOSKOW: Objection to form.
A. I think -- it's my understanding the utility of the 110-milligram dose is a reduction in bleeds.
Q. Right.
A. And so therefore, in some patients, the benefit/risk ratio was better, not because of increased stroke reduction, but because of decreased bleeds.
Q. So back to my question.

HARVEY

Is it your understanding that the 110-milligram dose prevents significantly less strokes than the 150-milligram dose?

MR. MOSKOW: Objection to form.

A. I -- I can't agree with that the way it's worded.

Q. Did you know that the FDA declined to approve the 110 dose because it concluded that there was no patient group it could find for whom the 110 was better than the 150?

A. I read that as their conclusion; however, in the documents, they said by traditional analysis, they should approve the 110 dose because the benefits do outweigh the risks.

Q. Okay.

A. However -- and then they had the conclusion.

Q. They thought the 150 was better?

A. They thought the 150 was better.

Q. For all patients?

A. That's what they thought at the time.

Q. Have they ever publicly changed that view?

HARVEY

A. Not as of today.

MR. SCHMIDT: Thank you. That's all.

MR. MOSKOW: I have one question.

EXAMINATION

BY MR. MOSKOW:

Q. Doctor, you were just asked about the universe of documents you had access to. What, if any, access did you have to a database of the 44 million plus pages of documents that have been produced in this litigation?

A. Well, when I referred to Dropbox, I was using that in a more general term, which meant on the web.

There was a -- there were many documents that were available and in a form where you had to enter a password and so I just assumed that was all part of the Dropbox. But, you know, that might have been -- you know, it was a different site so it was -- you know, I had access to many documents, some of which needed the -- the password.

MR. MOSKOW: Nothing further.

HARVEY

EXAMINATION

BY MR. SCHMIDT:

Q. Doctor, is it your understanding you had access to the full 44 plus million pages of documents that Mr. Moskow just referenced?

A. That's my understanding.

Q. And did you purport to review those documents in any way?

Did you -- is it your testimony that you did any kind of review of those documents to identify the important ones?

A. I -- I -- I didn't review all 44,000 documents.

MR. MOSKOW: 44 million.

THE WITNESS: 44 million.

MR. SCHMIDT: We'll stop there.

THE VIDEOGRAPHER: This concludes the video recorded deposition of Dr. Brian Harvey. We're off the record at 7:47.

(Deposition adjourned at 7:47 p.m.)

HARVEY

C E R T I F I C A T E

DISTRICT OF COLUMBIA:

I, MARY ANN PAYONK, shorthand reporter, do hereby certify that the witness whose deposition is hereinbefore set forth was duly sworn, and that such deposition is a true, correct, and full record of the testimony given.

I further certify that I am not related to any of the parties to this action by blood or by marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 1st day of December, 2017.

_____

MARY ANN PAYONK, Shorthand Reporter

HARVEY

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HARVEY

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Index (Cont'd.):

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Page/Line	Text of the Question
457 17	Do you see where she proposes language that references an over dosage range, he corrects it to say instead "patients are at a higher risk of bleeding," and she agrees to his correction?

<<INDEX END>>

NAME OF CASE: McDevitt vs. Boehringer
DATE OF DEPOSITION: November 30, 2017

1. To clarify the record.
2. To conform to the facts.
3. To correct transcription error.

Page _____ Line _____ Reason _____
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_____
DR. BRIAN HARVEY

SUBSCRIBED AND SWORN TO BEFORE ME
THIS _____ DAY OF _____, 2017.

_____
(Notary Public)
My Commission expires: _____